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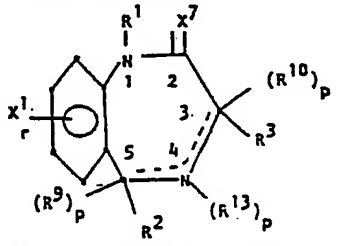
(54) Benzodiazepine derivatives and pharmaceutical compositions containing them.

(57) Benzodiazepine analogs of the formula:



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are disclosed which are antagonists of cholecystokinin (CCK).

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TITLE OF THE INVENTION

Benzodiazepine derivatives and pharmaceutical compositions containing them.

CROSS-REFERENCE

Starting materials for the compounds of Formula I are described in patent application U.S.S.N. 624,853, filed June 26, 1984, entitled "Acylaminophenylketones and Amines", which is incorporated herein by reference.

This is a CIP of U.S.S.N. 705,272 filed February 25, 1985 which in turn is a CIP of U.S.S.N. 624,854, filed June 26, 1984.

BACKGROUND OF THE INVENTION

Cholecystokinin (CCK) is a neuropeptide composed of thirty-three aminoacids in its originally isolated form. See: Mutt and Jorpes, Biochem. J. 125 678 (1971). Also occuring in circulation are 39, 12, and 8 amino acid forms. The carboxyl terminal octapeptide (CCK-8) is the minimum fully active

sequence. Gastrin occurs in 34, 17 and 14 amino acid forms in circulation and is related to CCK by indentity of the C-terminal pentapeptides Gly-Trp-Met-Asp-Phe-NHR_2 gastrin and CCK exist in both gastrointestinal tissue and the central nervous system. V. Mutt, Gastrointestinal Hormones, G. B. J. Glass, Ed., Raven Press, N.Y., p. 169 and G. Nisson, ibid, p. 127. CCK is believed to play an important role in appetite regulation and CCK may be a physiological satiety hormone. G. P. Smith, Eating and Its Disorders, A. J. Stunkard and E. Stellar, Eds, Raven Press, New York, 1984, p. 67.

Among additional effects of CCK are stimulation of colonic motility, stimulation of gall bladder contraction, stimulation of pancreatic enzyme secretion, and inhibition of gastric emptying. CCK reportedly co-exists with dopamine in certain mid-brain neurons and thus may also play a role in the functioning of dopaminergic systems in the brain, as well as serving as a neurotransmitter in its own right. See: A. J. Prange et al., "Peptides in the Central Nervous System", Ann. Repts. Med. Chem. 17 31, 33 (1982) and references cited therein; J. A. Williams, Biomed. Res. 3 107 (1982); and J. E. Morley, Life Sci. 30, 479, (1982).

The primary role of gastrin appears to be stimulation of secretion of water and electrolytes from the stomach and it is therefore involved in control of gastric acid secretion.

CCK antagonists are useful in the treatment and prevention of CCK-related disorders of the gastrointestinal, central nervous and appetite regulatory systems of animals, especially humans. CCK

antagonists are also useful in potentiating and prolonging opiate mediated analgesia and thus have utility in the treatment of pain [see P.L. Faris et al., Science 226, 1215 (1984)]. Three distinct chemical classes of CCK receptor antagonists have been reported. One class comprises derivatives of cyclic nucleotides; detailed structure-function studies have demonstrated that of the various members of this class, dibutyryl cyclic GMP is the most potent. See; N. Barlos et al., Am. J. Physiol., 242, G 161 (1982) and P. Robberecht et al., Mol., Pharmacol., 17, 268 (1980). The second class comprises peptide antagonists which are C-terminal fragments and analogs of CCK. Recent structure-function studies have shown that both shorter C-terminal fragments of CCK (Boc-Met-Asp-Phe-NH_2; Met-Asp-Phe-NH_2) as well as longer CCK fragments Cbz-Tyr(SO_3H)-Met-Gly-Trp-Met-Asp-NH_2) can function as CCK antagonists. See: R. T. Jensen et al., Biochem. Biophys. Acta., 757, 250 (1983) and M. Spanarkel et al., J. Biol. Chem., 258, 6746 (1983). The latter compound was recently reported to be a partial agonist [see J. M. Howard et al., Gastro-enterology 86(5) Part 2, 1118 (1984)]. The third class of CCK receptor antagonists comprises the amino acid derivatives; proglumide, a derivative of glutaramic acid, and the N-acyl tryptophans including para-chlorobenzoyl-L-tryptophan (benzotript). See W. F. Hahne et al., Proc. Natl. Acad. Sci. U.S.A., 78, 6304 (1981) and R. T. Jensen et al., Biochem. Biophys. Acta., 761, 269 (1983). All of these compounds are relatively weak antagonists of CCK (IC_{50}: 10^{-4}-10^{-6}M; generally, 10^{-4}M but down

to 10^{-6}M in the case of peptides). The peptide antagonists have substantial stability and absorption problems.

Gastric antagonists are useful in the treatment and prevention of gastrin-related disorders of the gastrointestinal system in humans and animals such as ulcers, Zollinger-Ellison syndrome, entral G cell hyperplasia and other conditions in which reduced gastrin activity is of therapeutic value. There are no effective receptor antagonists of the *in vivo* effects of gastrin. J. S. Morley, *Gut Pept. Ulcer Proc.*, Hiroshima Symp. 2nd, 1983, p. 1. Very weak *in vitro* antagonists such as proglumide and certain peptides have been reported, J. Martinez, *J. Med. Chem.*, *27*, 1597 (1984).

The benzodiazepine (BZD) structure class has been widely exploited as therapeutic agents, especially as central nervous system (CNS) drugs. These compounds exhibit strong binding to "benzodiazepine receptors" *in vitro*, but have not been reported to bind to CCK or gastrin receptors. Benzodiazepines have been shown to antagonize CCK-induced activation of rat hippocampal neurones but this effect is mediated by the benzodiapine receptor, not the CCK receptor [see J. Bradwejn *et al.*, *Nature*, *312*, 363 (1984)]. The large majority of reported BZD's do not contain substituents attached to the 3-position of the seven membered ring. It is well known in the art that 3-substituents result in decreasing CNS activity, especially as these substituents increase in size. It has been demonstrated that the preferred stereochemistry at position 3 for CNS activity is *S*, which would

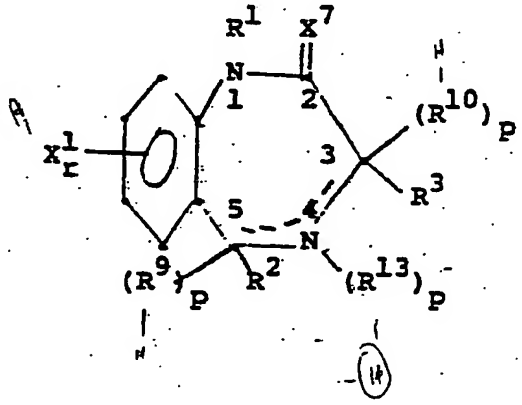
correspond to an L-amino acid such as L-tryptophan. The compounds of Formula I are distinguished from BZD's of the prior art especially by the presence of 3-substituents. The Formula I compounds bind strongly to CCK receptors, but only weakly to BZD receptors, especially with increasing size of the substituent. The preferred stereochemistry of Formula I compounds is opposite to that of prior art BZD's.

SUMMARY OF THE INVENTION

It has now been found that compounds of Formula I are antagonists of cholecystokinin (CCK) and bind specifically to the CCK receptor. These CCK antagonists are useful in the treatment and prevention of CCK-related disorders of the gastrointestinal, central nervous and appetite regulatory systems of mammals, especially humans. The compounds of Formula I are also gastrin antagonists. They are useful in the treatment and prevention of gastrointestinal ulcers, Zollinger-Ellison syndrome, antral G cell hyperplasia, and other conditions in which reduced gastrin activity is of therapeutic value.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are those of Formula I:

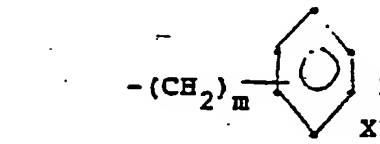


I

wherein

R^1 is H, C_1-C_5 linear or branched alkyl, loweralkenyl, loweralk; $-(CH_2)_mCOOR^6$, $-(CH_2)_n$-cycloloweralkyl, $(CH_2)_m-CN$, $-(CH_2)_mNR^4R^5$, $-(CH_2)_m-CONR^4R^5$, or $(CH_2)_nCX_3^{10}$;

R^2 is H, loweralkyl, substituted or unsubstituted phenyl (wherein the substitutents may be 1 or 2 of halo, loweralkyl, loweralkoxy, loweralkylthio, carboxyl, carboxyloweralkyl, nitro, $-CF_3$, or hydroxy),



$-(CH_2)_mSCH_3$,

$-(CH_2)_mSOCH_3$, $-(CH_2)_mSO_2CH_3$, or $-(CH_2)_mCOOR^6$;

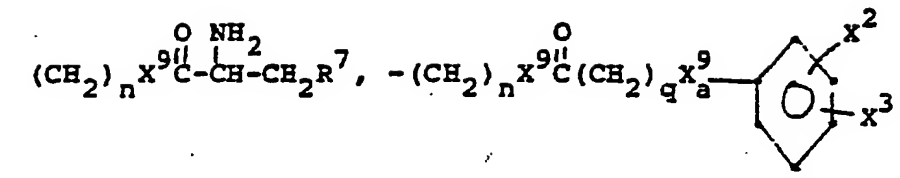
R^3 is $-(CH_2)_nR'$, $-(CH_2)_nCHR^7$, $-(CH_2)_nC(OH)R^7$

$-(CH_2)_nCR^7$, $-(CH_2)_nNR^{18}(CH_2)_qR^7$

$-(CH_2)_nNR^{18}CHCOOR^6$, $-(CH_2)_nX^9C(CH_2)_qR^7$,

$-NH(CH_2)_{2-3}NHR^7$, $-NH(CH_2)_{2-3}NHCOR^7$,

$-(CH_2)_nX^9CCHCH_2R^7$, $-(CH_2)_nX^9$  $-R^7$,

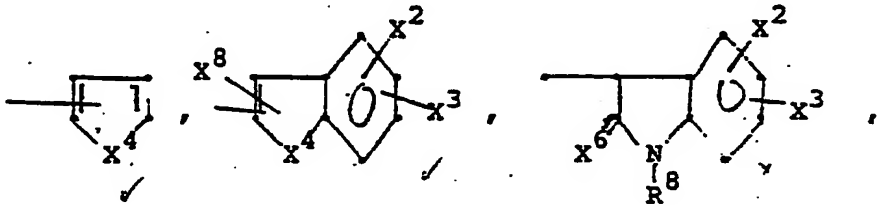


$-(CH_2)_n-NR^{18}SO_2-(CH_2)_qR^7$ or $-CHR^7$;

R^4 and R^5 are independently H, loweralkyl, or cycloloweralkyl;

R^6 is H, loweralkyl, cycloloweralkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted phenylloweralkyl wherein the phenyl or phenylloweralkyl substituents may be 1 or 2 of halo, loweralkyl, loweralkoxy, nitro, or CF_3;

R^7 and R_a^7 are independently α- or β-naphthyl,



substituted or unsubstituted phenyl (wherein the substituents may be 1 to 2 of halo, $-NO_2$, $-OH$, $-NR^4R^5$, CF_3, CN, SCF_3, $CH{\equiv}C$, CH_2SCF_3, $OCCH_3$, $OCHF_2$, SH, SØ, PO_3H, loweralkyl, loweralkoxy, or loweralkylthio),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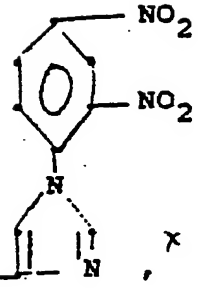
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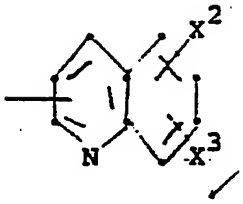
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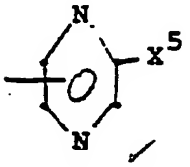
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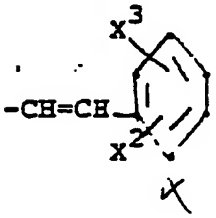
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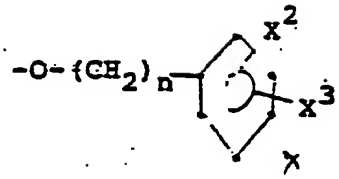

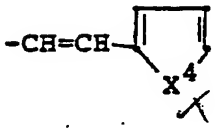
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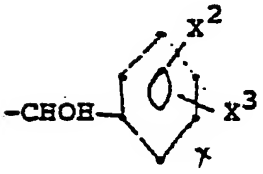
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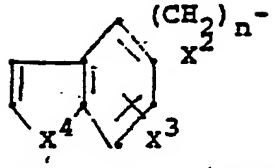
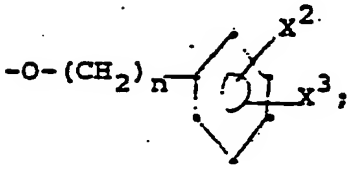
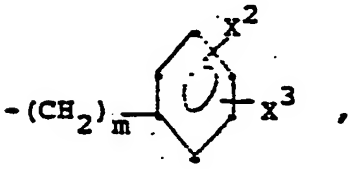


with the provisos that q is not 0 or 1 in $-(CH_2)_nNH(CH_2)_qR^7$ and that q is not 0 in

$-(CH2)_nNR^{18}\underset{\displaystyle (CH_2)_q}{\overset{\displaystyle R^7}{CH}}COOR^6$ when R^7 or R_a^7 is



R^8 is H, loweralkyl, cycloloweralkyl, $-(CH_2)_m-CONH_2$, $-(CH_2)_mCOOR^6$, $-(CH_2)_n$-cycloloweralkyl, $-(CH_2)_mNR^4R^5$,



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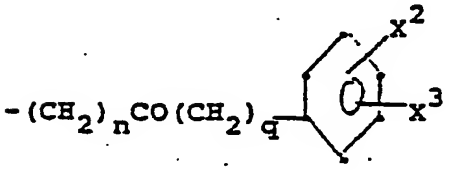
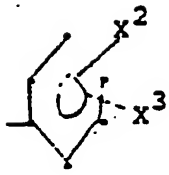
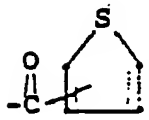


, or

$-COCHNHCOOR^{11}$;
$\quad\quad CH_2R^{12}$

R^9 and R^{10} are independently H, -OH, or $-CH_3$;
R^{11} and R^{12} are independently loweralkyl or cycloloweralkyl;
R^{13} is H, O, loweralkyl, acyl, or cycloloweralkyl;
R^{14} is loweralkyl or phenylloweralkyl;

R^{15} is H, loweralkyl,  , or $-NR^{16}R^{17}$;

R^{16} and R^{17} are independently H, or  ;

R^{18} is H, loweralkyl or acyl;

m is 1-4;

n is 0-4;

p is 0 when its adjacent --- is unsaturated and 1 when its adjacent --- is saturated except that when R^{13} is O, p=1 and --- is unsaturated;

q is 0-4;

r is 1 or 2;

X^1 is H, $-NO_2$, CF_3 CN, OH, loweralkyl, halo, loweralkylthio, loweralkoxy, $-(CH_2)_nCOOR^6$, $O-\overset{O}{\overset{\|}{C}}-R^4$ or $-NR^4R^5$;

X^2 and X^3 are independently H, -OH, $-NO_2$, halo, loweralkylthio, loweralkyl, $O-\overset{O}{\overset{\|}{C}}-R^4$ or loweralkoxy;

X^4 is S, O, CH_2 or NR^8;

X^5 is H, CF_3, CN, $-COOR^6$, NO_2, or halo;

X^6 is O or HH;

X^7 is O, S, HH, or NR^{15} with the proviso that X^7 can be NR^{15} only when R^1 is not H;

X^8 is H, loweralkyl;

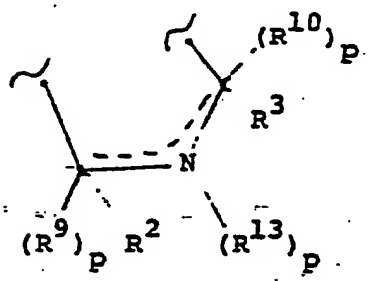
X^9 and X^9_a are independently NR^{18}; O;

X^{10} is F, Cl, or Br;

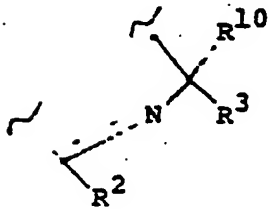
--- is a saturated or unsaturated bond

and the pharmaceutically acceptable salts thereof.

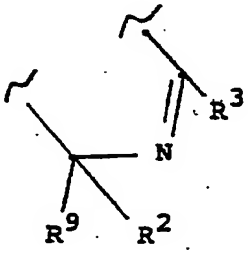
As used herein, the definition of each expression, e.g. m, n, p, loweralkyl, etc., when it occurs more than once in any structure, is intended to be independent of its definiton elsewhere in the same structure. Thus, the ring fragment

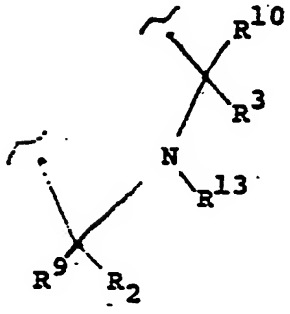


, since each p is independently 1 or 0, represents the three structures



, and





, when R^{13} is not O.

In the compounds of Formula I, the preferred stereochemistry relates to D-tryptophan, where C^2 and N^4 of Formula I correspond to the carbonyl

carbon and α-amino N of D-tryptophan and R^3 occupies the position of the indolylmethyl side chain.

As used herein, halo is F, Cl, Br; or I; loweralkyl is 1-4 carbon straight or branched chain alkyl and includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and t-butyl; in loweralkoxy and loweralkylthio, the alkyl portion is loweralkyl as previously defined; cycloloweralkyl is cycloalkyl of 3-5 carbons; loweralkenyl is 1-5 carbon straight or branched chain alkenyl; acyl is formyl, acetyl propionyl, or butyryl; loweralkynyl is 1-5 carbon straight or branched chain alkynyl.

The pharmaceutically acceptable salts of the compounds of Formulas I include the conventional non-toxic salts or the quarternary ammonium salts of the compounds of Formula I formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the compounds of Formula I which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with

an excess of the desired salt forming inorganic or organic acid or base in a suitable solvent or various combinations of solvents.

The pharmaceutically acceptable salts of the acid of Formula I are also readily prepared by conventional procedures such as treating an acid of Formula I with an appropriate amount of a base, such as an alkali or alkaline earth metal hydroxide e.g. sodium, potassium, lithium, calcium, or magnesium, or an organic base such as an amine, e.g., dibenzyl-ethylenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like, or a quaternary ammonium hydroxide such as tetramethylammonium hydroxide and the like.

An embodiment of this invention is the preparation of compounds of Formula I.

Another embodiment is the use of the compounds of Formula I for the treatment and the prevention of disorders of the gastrointestinal, central nervous, and appetite regulatory systems of mammals, especially of man. Specifically, the Formula I compounds are useful in treatment and prevention of disorders of gastric acid secretion, gastrointestinal motility, pancreatic secretions, and dopaminergic functions. The compounds of Formula I are especially useful in the prevention and treatment of irritable bowel syndrome.

A further embodiment is a composition comprising an effective amount of a compound of Formula I and a pharmaceutically acceptable carrier.

The ability of the compounds of Formula I to antagonize CCK and gastrin makes these compounds useful as pharmaceutical agents. These compounds

will be especially useful in the treatment and prevention of disease states wherein CCK or gastrin may be involved, for example, gastrointestinal disorders such as irritable bowel syndrome, ulcers, excess pancreatic or gastric secretion, acute pancreatitis, motility disorders, pain (potentiation of opiate analgesia), central nervous system disorders caused by CCK's interaction with dopamine such as neuroleptic disorders, tardive dyskinesia, Parkinson's disease, psychosis or Gilles de la Tourette Syndrome, disorders of appetite regulatory systems, Zollinger-Ellison syndrome, and antral G cell hyperplasia.

The compounds of Formula I or pharmaceutically acceptable salts thereof, can be administered to a human subject either alone, or preferably, in combination with pharmaceutically acceptable carriers or diluents, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally. Parenteral administration includes intravenous, intramuscular, intraperitoneal, subcutaneous and topical administration.

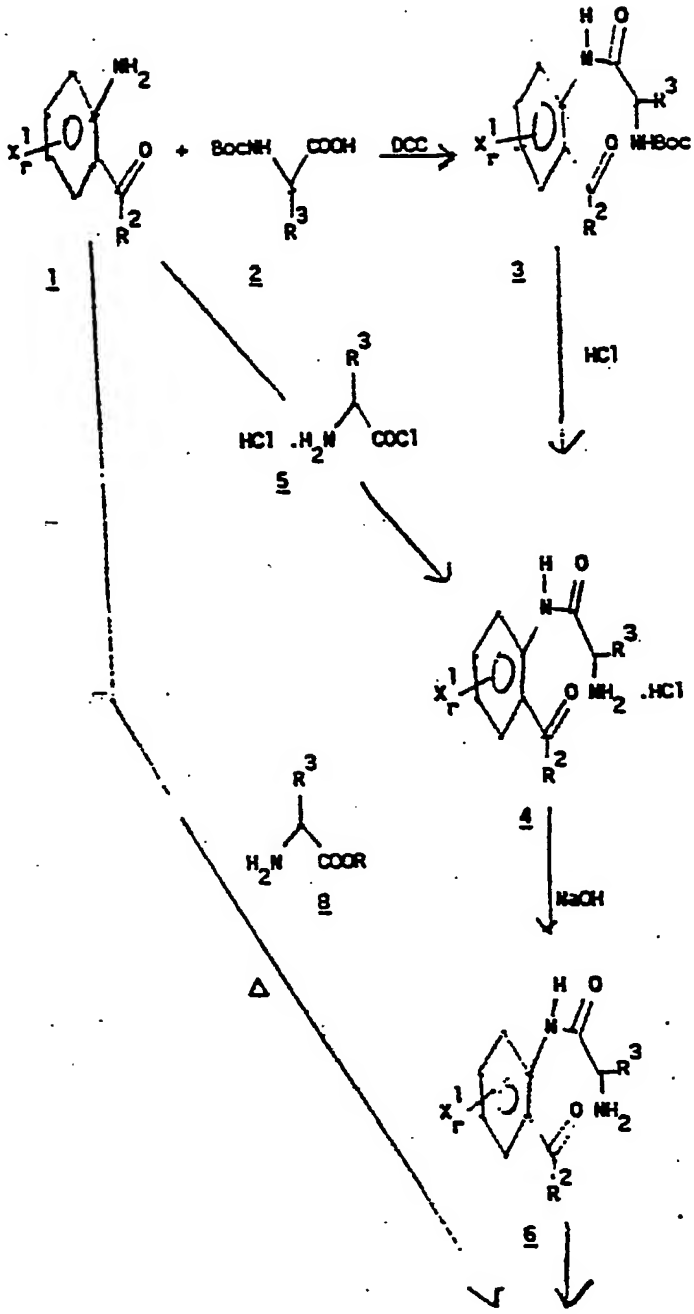
For oral use of an antagonist of CCK or gastrin of this invention, the selected compound can be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents are lactose and dried corn starch. When aqueous

suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents can be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled to render the preparation isotonic.

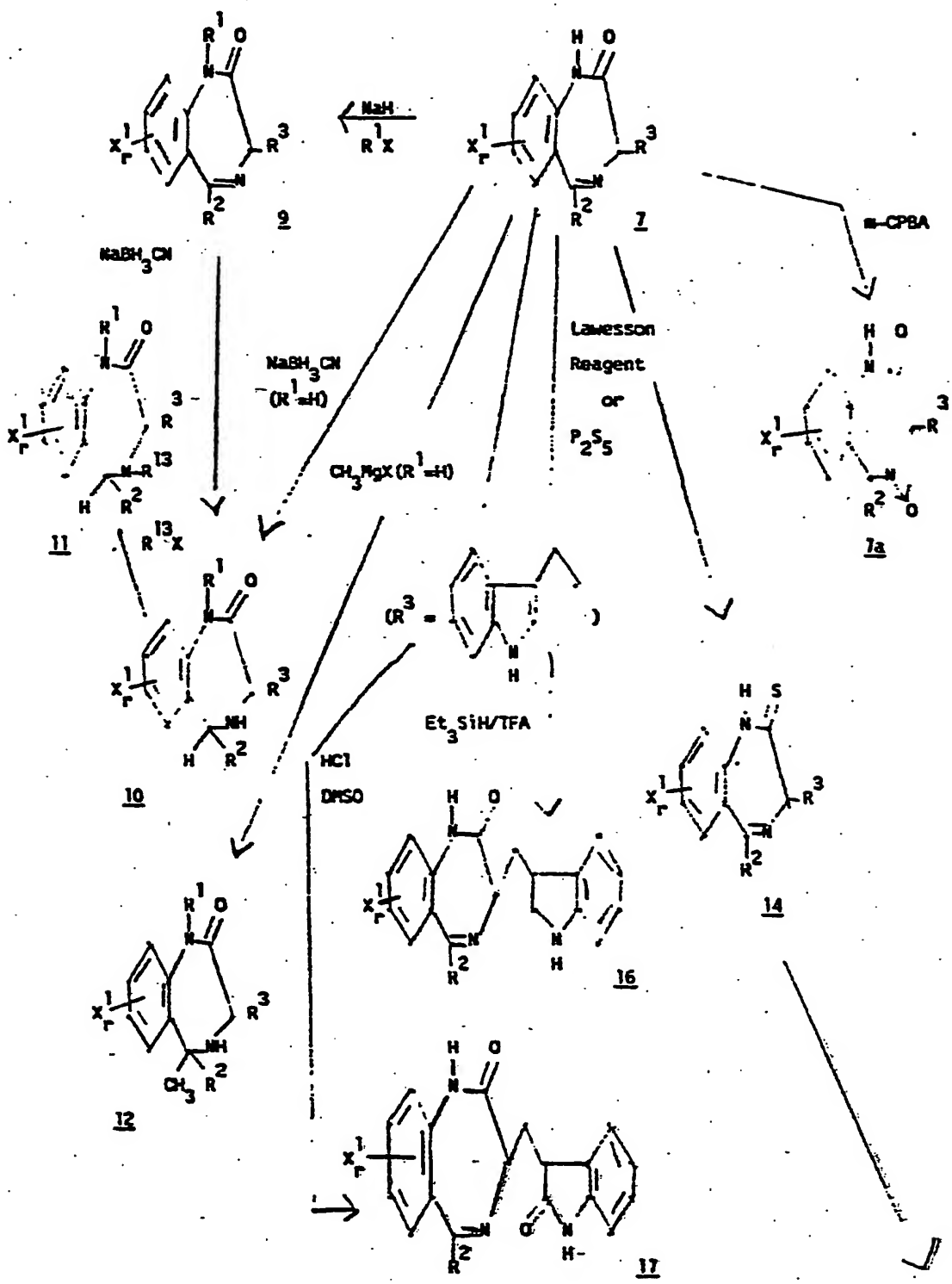
When a compound of Formula I or a salt thereof is used as an antagonist of CCK or gastrin in a human subject, the daily dosage will normally be determined by the prescribing physician. Moreover, the dosage will vary according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms. However, in most instances, an effective daily dosage will be in the range from about 0.05 mg to about 50 mg/kg and preferably 0.5 mg to about 20 mg/kg in a single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

The compounds of Formula I are prepared according to the following schemes.

REACTION SCHEME I



REACTION SCHEME I (Cont'd)



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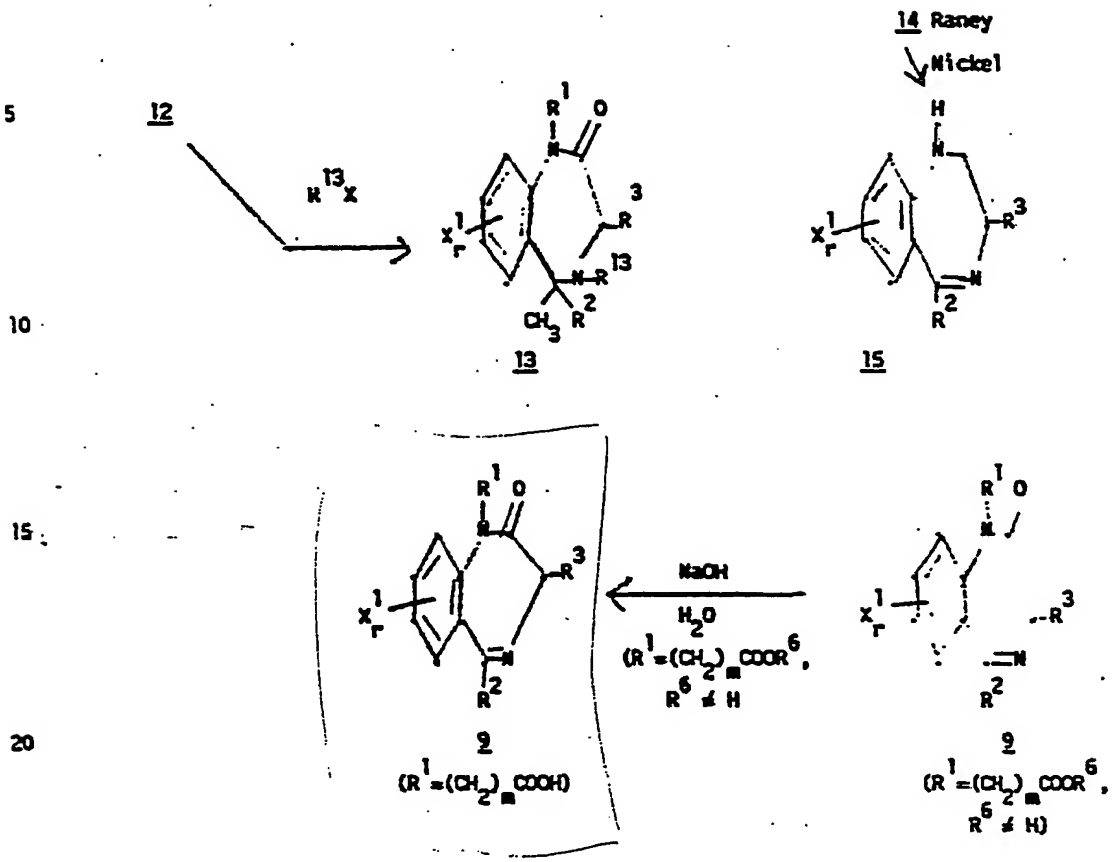
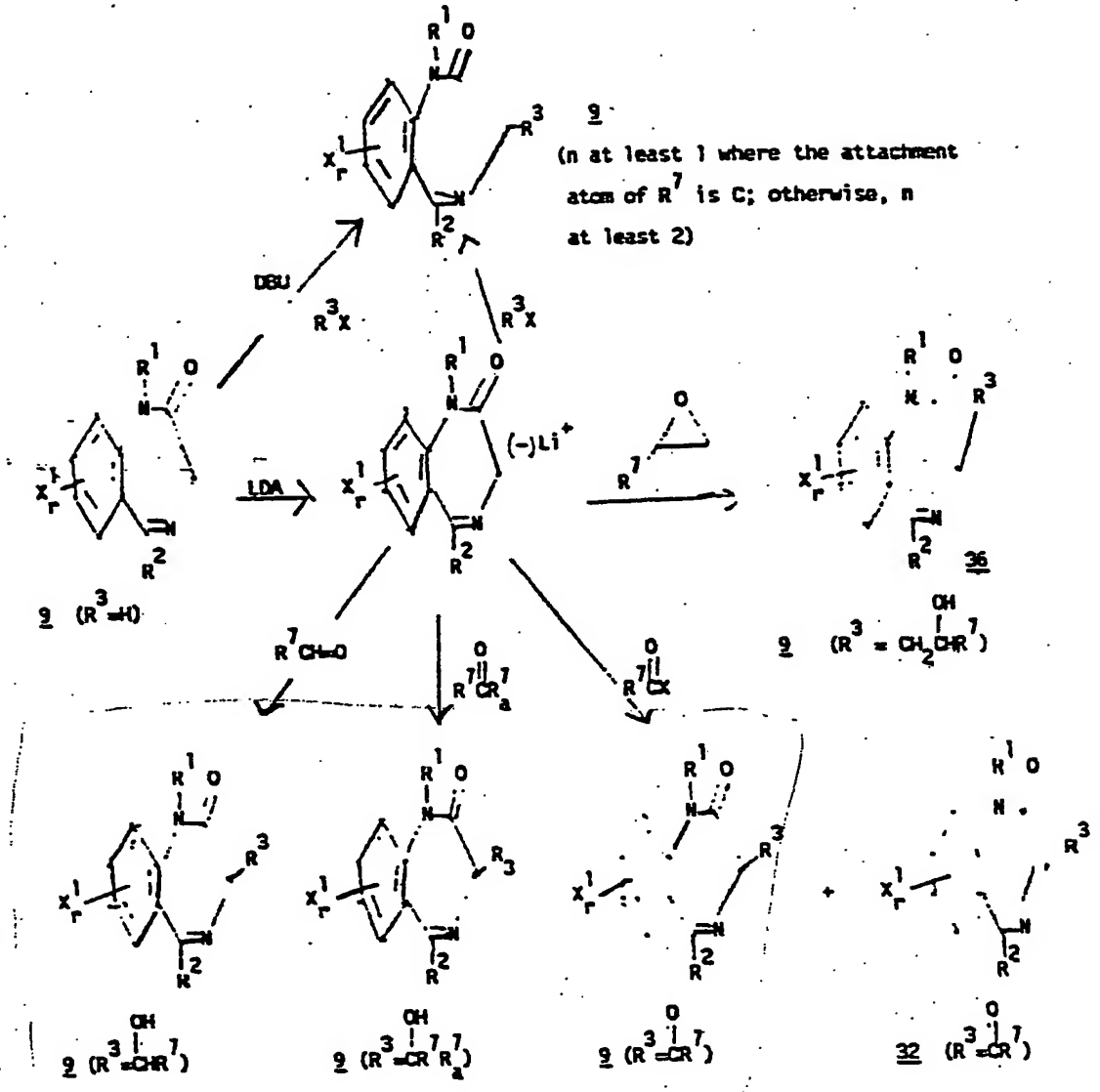


REACTION SCHEME II



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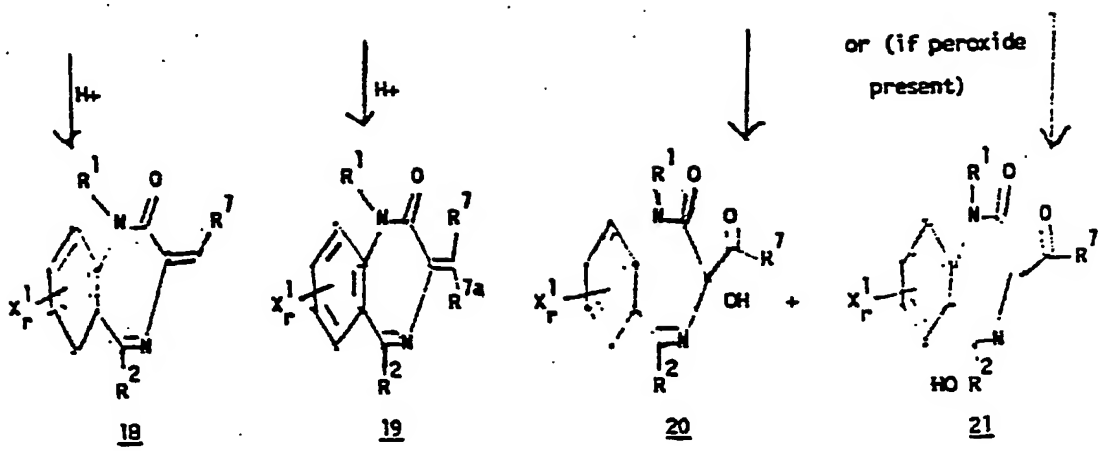
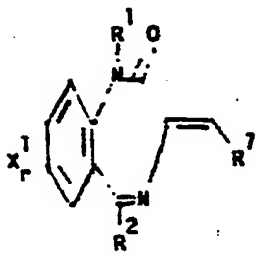
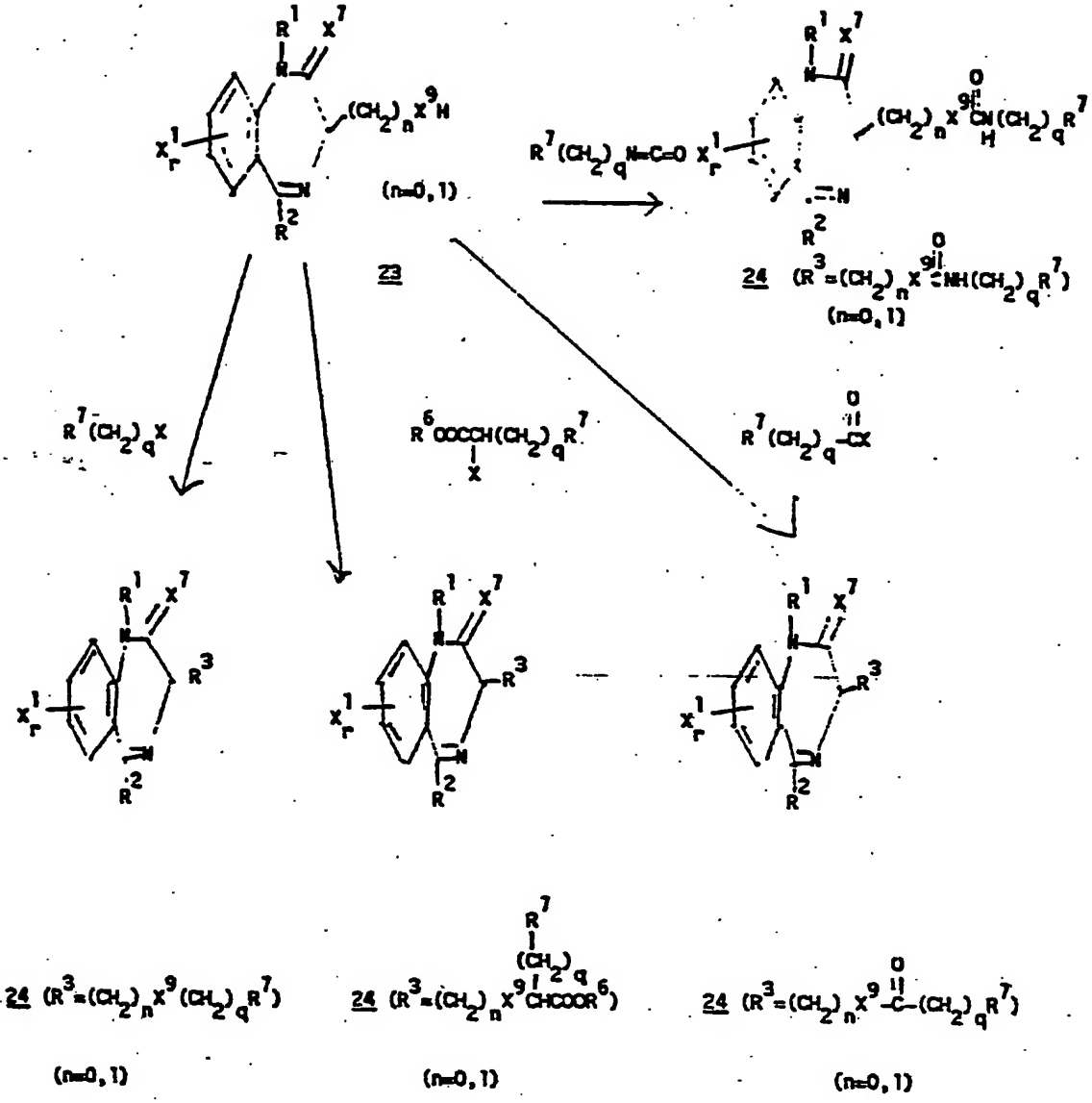


18 19 20 21

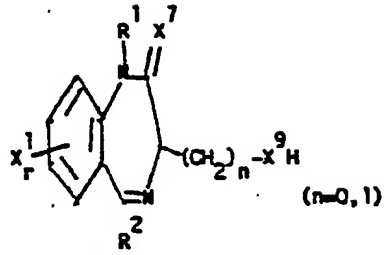


22

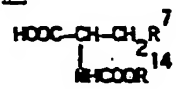
REACTION SCHEME III



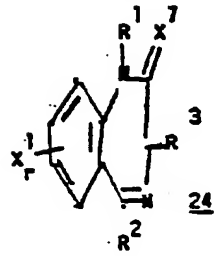
REACTION SCHEME IIIa



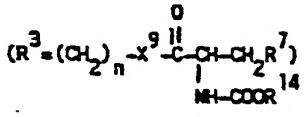
23



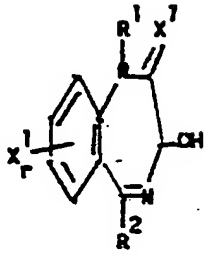
DCC, EDC or i-BuOCOCl



24

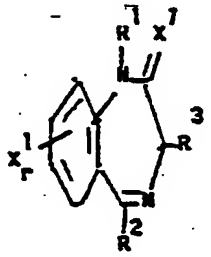


REACTION SCHEME IIIb



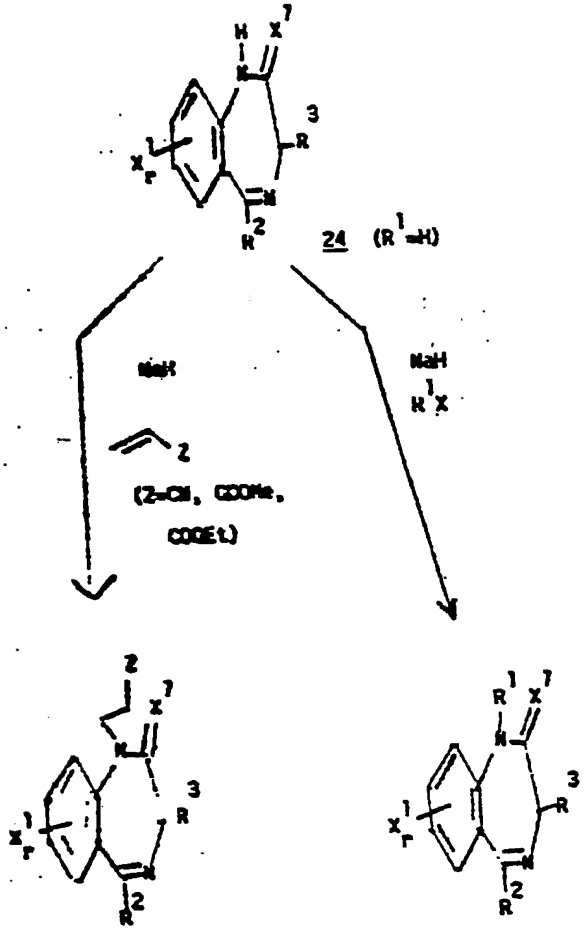
24 (R^3=OH)

$R^7(CH_2)_q\overset{O}{\overset{\|}{C}}X$ X=halo



24 (R^3=$O\overset{O}{\overset{\|}{C}}(CH_2)_qR^7$)

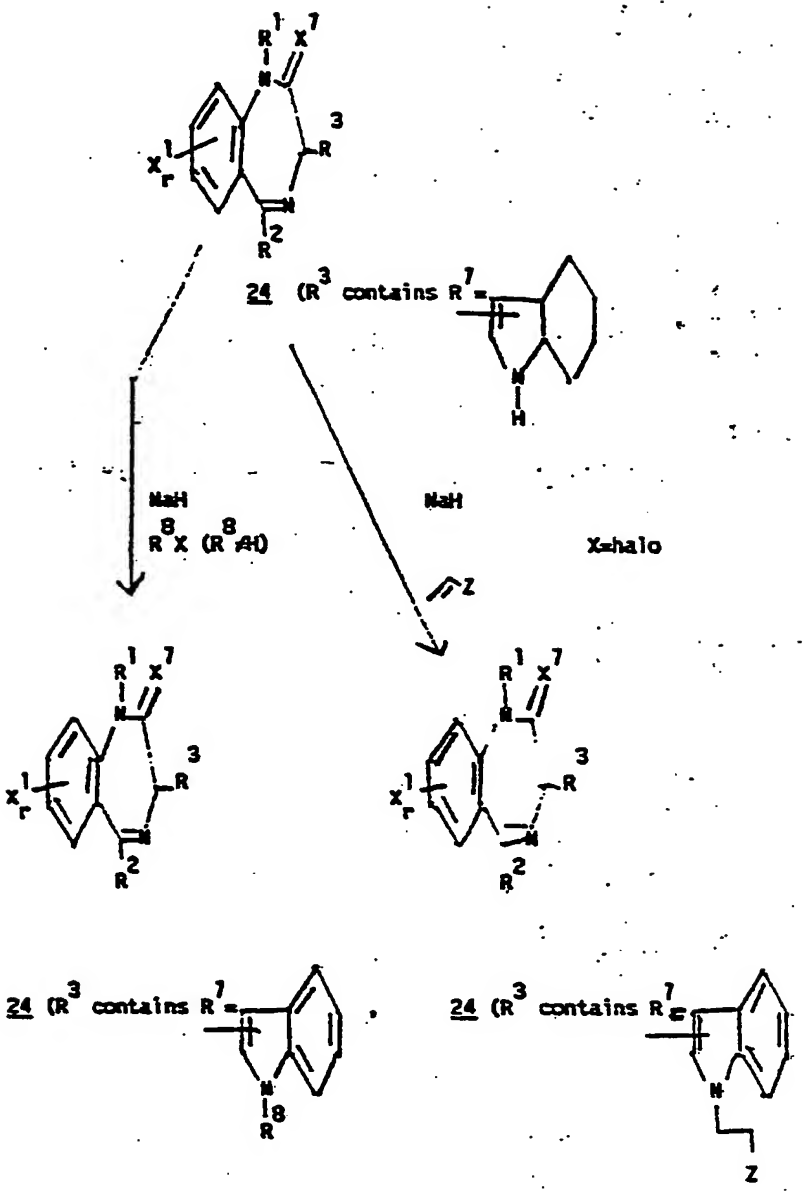
REACTION SCHEME IIIc



24 (R^1=H)

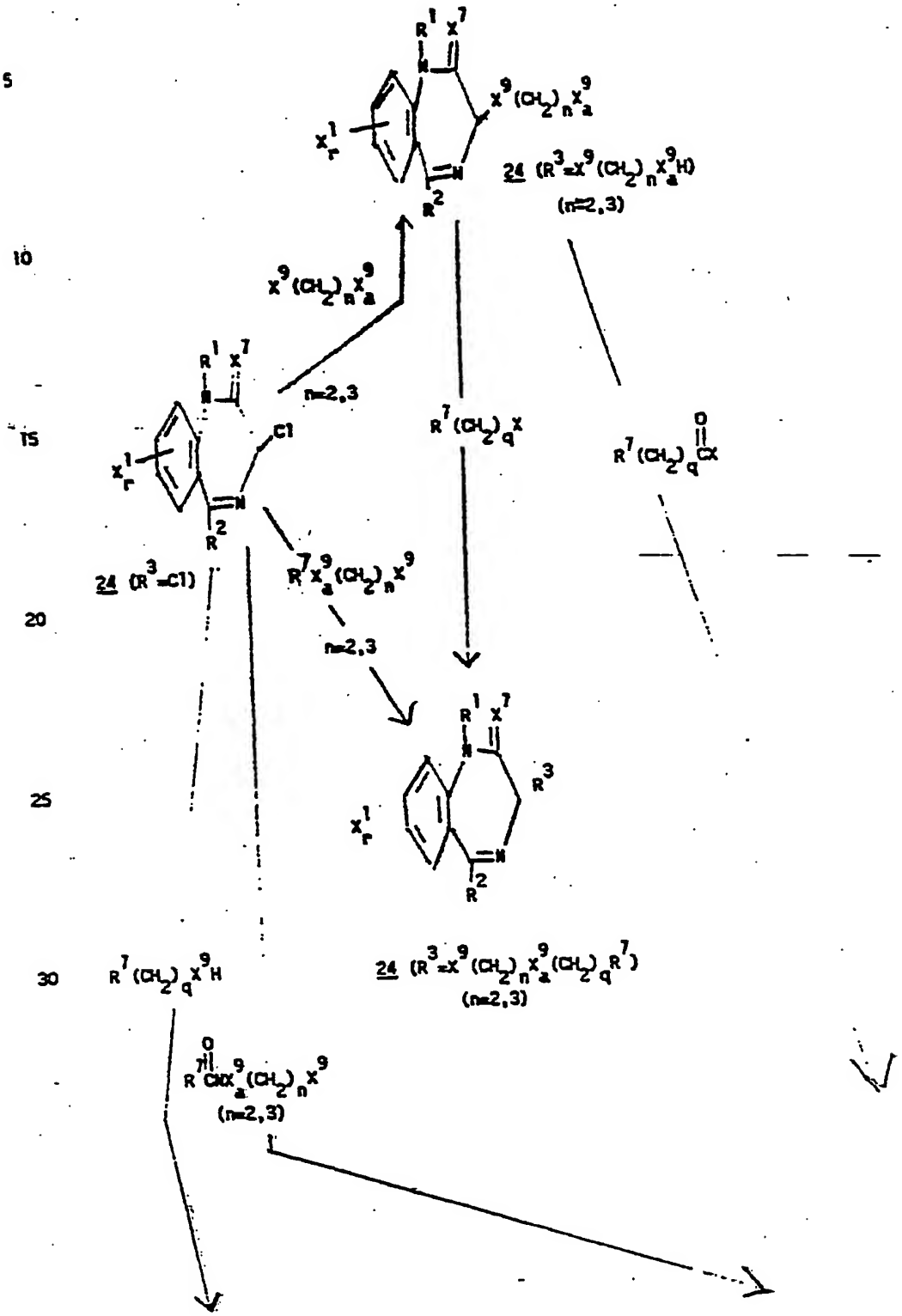
24 (R^1= ⌒Z, Z=CN, COOMe, COOEt) 24

REACTION SCHEME IIId



Where, in the 24 compound, R^1 and/or R^8 is an ester [$(CH_2)_m COO-C_1-C_3$ alkyl] moiety, this group can be conventionally hydrolyzed to obtain the corresponding acid moiety or treated with NH_3 to obtain the corresponding amide moiety.

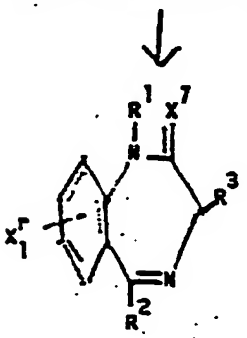
REACTION SCHEME IV



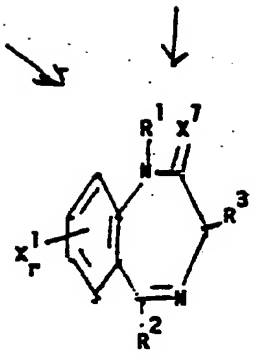
1711918

0167919

REACTION SCHEME IV (cont'd)

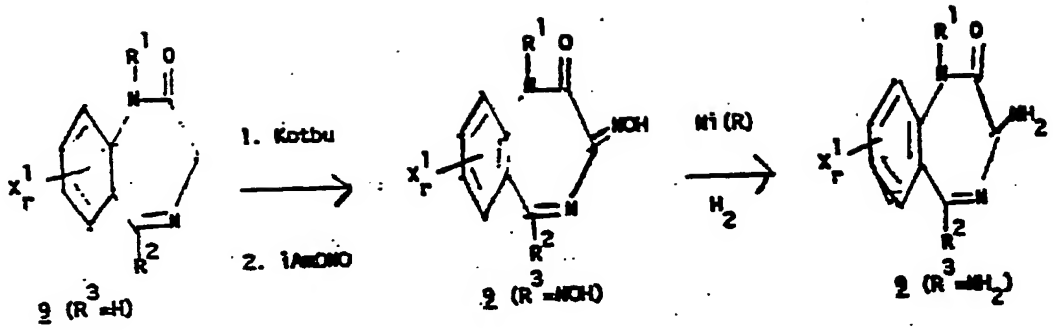


24 (R^3=$X^9(CH_2)_qR^7$)



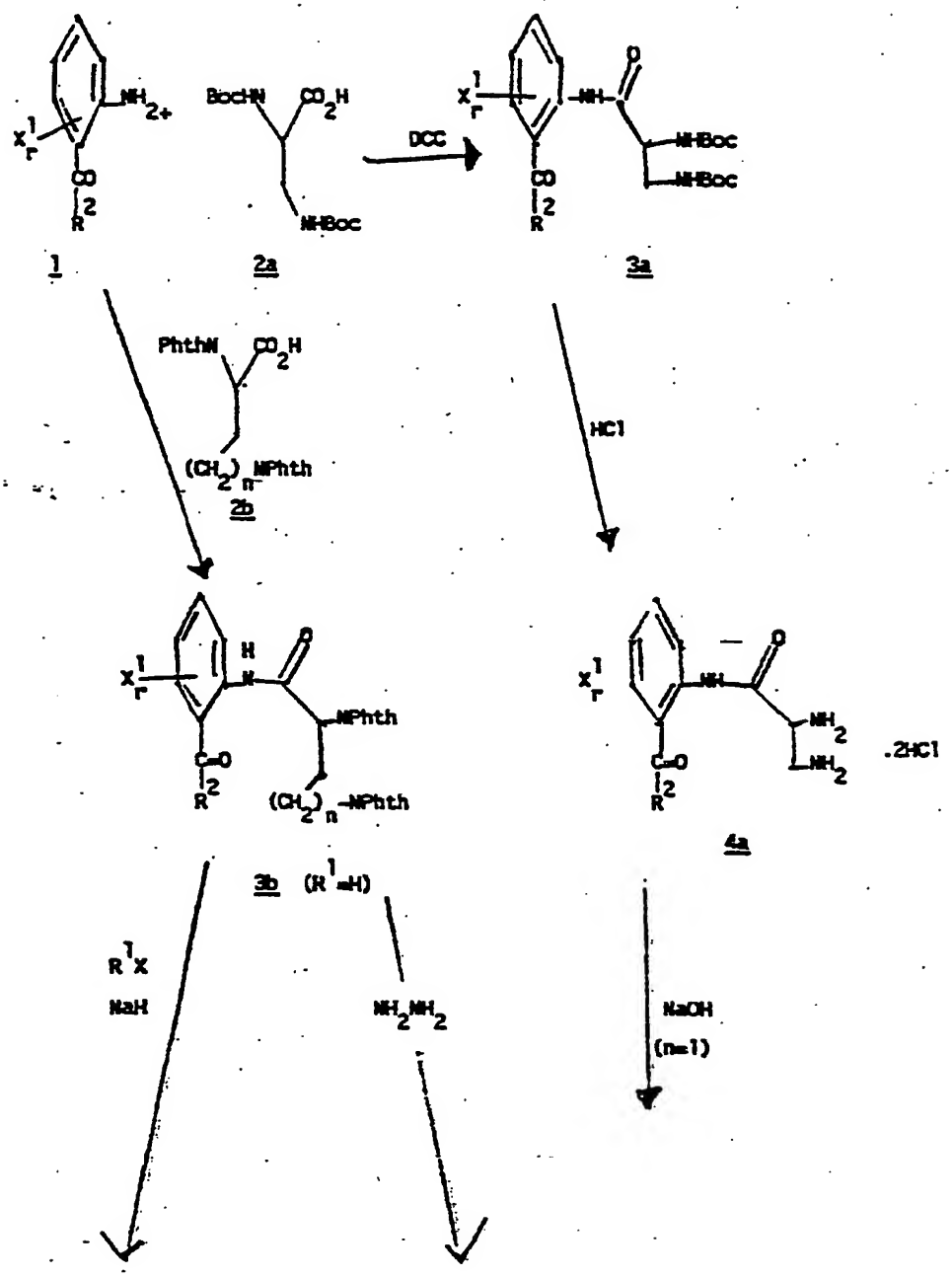
24 (R^3=$X^9(CH_2)_nX^9_aC(=O)(CH_2)_qR^7$)
(n=2,3)

SCHEME IVa

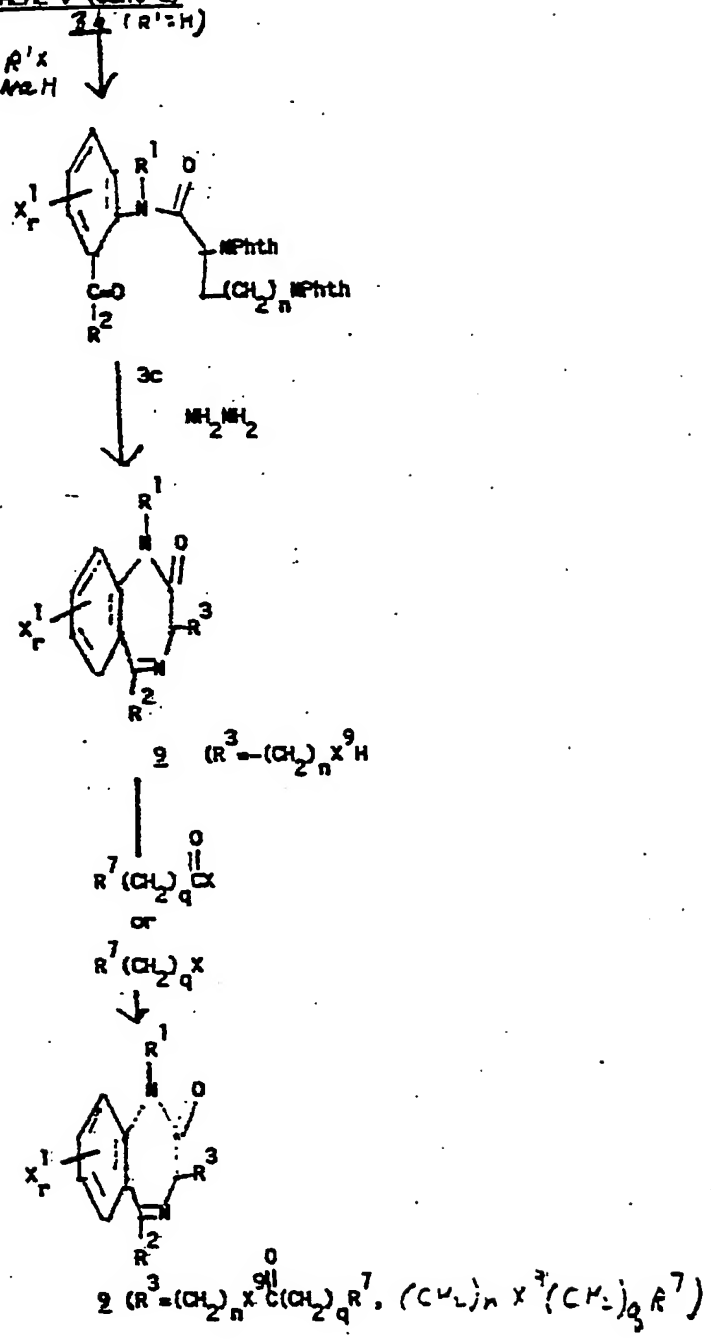


9 (R^3=H) 2 (R^3=NOH) 2 (R^3=NH_2)

REACTION SCHEME V

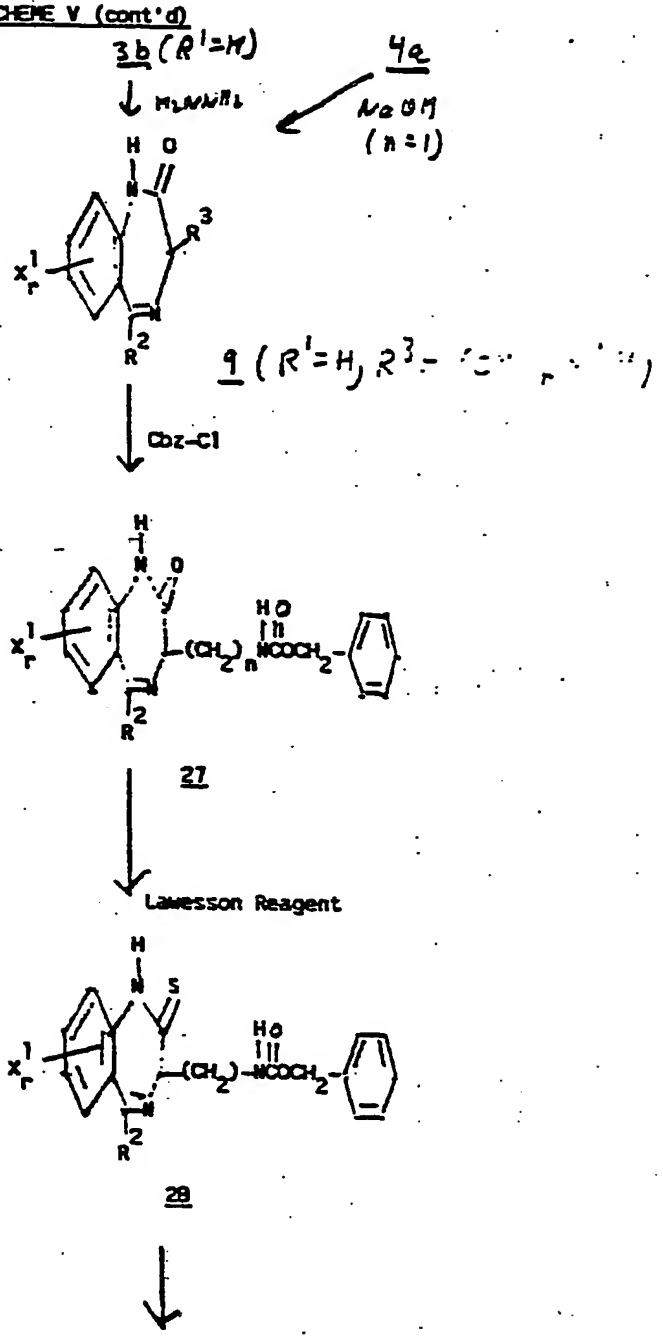


REACTION SCHEME V (cont'd)



9 (R^3=$(CH_2)_n X^9 C(CH_2)_q R^7$, $(CH_2)_n X^9 (CH_2)_q R^7$)

REACTION SCHEME V (cont'd)



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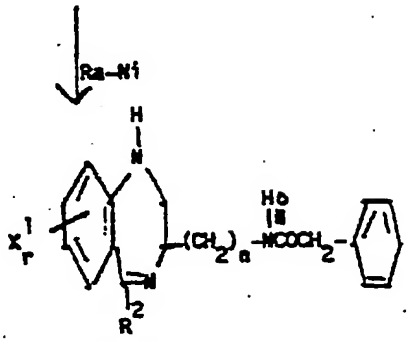

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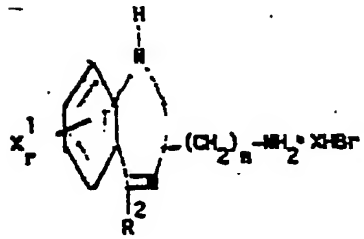

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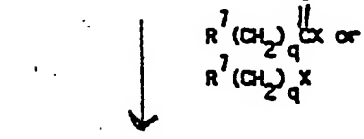
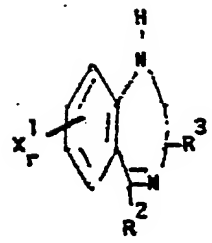
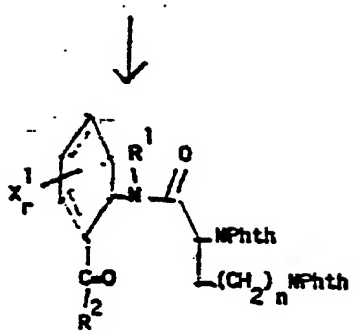




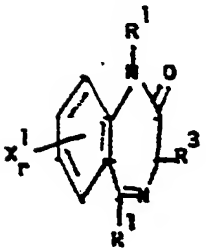
31

REACTION SCHEME V (cont'd)



3c

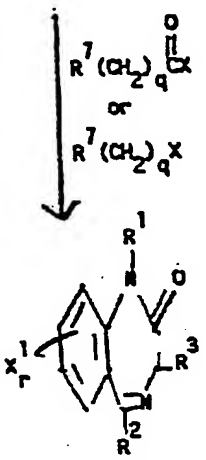
NH_2NH_2



9 (R^3=$-(CH_2)_nX^9H$)

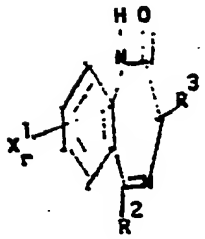
REACTION SCHEME V (cont'd)

9 ($R^3 = -(CH_2)_n X^9 H$)



9 ($R^3 = (CH_2)_n X^9 (CH_2)_q R^7$)

$(CH_2)_n X^9 C(=O)(CH_2)_q R^7$)



9 ($R^1 = H$, $R^3 = (CH_2)_n X^9 H$)

2-Aminoarylketones 1, (Scheme I) preferably 2-amino-benzophenones containing various substituents in the aryl rings, preferably halo substituents, are coupled to N-protected D-amino acids 2 (preferably, Boc-amino acids) using dicyclohexylcarbodiimide (DCC) or other conventional peptide coupling reagent. The product 3 is N-deprotected by treatment with acid, preferably anhydrous HCl in ethyl acetate, to give the α-aminoacyl derivative 4 of the 2-aminoarylketone. Alternatively, this same product is obtained by treatment of the 2-aminoarylketone 1 with the acid chloride hydrochloride 5 of the D-amino acid, which is prepared from the amino acid with PCl_5-AcCl.

Treatment of this α-aminoacyl derivative 4 with base, preferably aqueous sodium hydroxide in methanol, gives the free base 6 which is cyclized to the 3,5-disubstituted benzodiazepine 7 upon stirring in the methanolic base for 2-120 hours, preferably 48 hours. Alternatively, the 3,5-disubstituted benzodiazepine 7 is obtained by heating the 2-aminoarylketone 1 with the ester 8, preferably methyl or ethyl, of the D-amino acid, preferably in refluxing pyridine, for 2-48 hours, preferably for 18 hours.

Alternatively (Scheme V), the ketones 1 may be coupled with N-phthalylamino acids such as 2b to give the products 3b using DCC or other conventional peptide coupling reagent. 3b may be deprotected and cyclized to 9 (R^1=H, R^3=$(CH_2)_nX^9H$) by treating with hydrazine. Alternatively, 3b may be first alkylated by treatment with sodium hydride followed by an alkyl halide in dimethylformamide (DMF) to give the alkyl derivative 3c. Treating this product with hydrazine gives the N^1-alkylbenzodiazepine, 9 (R^3=$(CH_2)_nX^9H$).

9 (R^3=$(CH_2)_nX^9H$) are alkylated by treatment with alkyl halide or dialkyl sulfate or acylated by treatment with acid halides or anhydrides, preferably in the presence of base such as triethyl amine. The products are the alkyl and acyl derivatives 9 (R^3=$(CH_2)_nX^9(CH_2)_qR^7$ and R^3=$(CH_2)_nX^9\overset{O}{\overset{\|}{C}}(CH_2)_qR^7$).

Alternatively, protection of the 3-amino function in 9 (R^3=$(CH_2)_nNH_2$), preferably with benzylchloroformate affords the acyl derivative 27. Treatment of this material with P_2S_5 or preferably with Lawesson's reagent in toluene gives the thioamide 28 which is converted to the amine 29 with Raney nickel in ethanol. Deprotection of the resulting product 29 via hydrogenolysis, or preferably by the action of hydrobromic acid, yields the corresponding amino compound 30. Alkylation of 30 by treatment with alkyl halide or dialkyl sulfonate or acylation with carboxylic acid halide or carboxylic acid anhydride in the presence of an acid binding agent such as triethylamine or preferably with a carboxylic acid in the presence of a peptide coupling reagent such as dicyclohexyl-carbodiimide gives the alkyl or acyl derivatives 31.

3,5-Disubstituted benzodiazepines 7 (Scheme I) are also treated with sodium hydride in dimethylformamide (DMF), followed by an alkyl halide, to give the 1-alkyl derivatives 9. These or the parent 1-unsubstituted compound 7 are reduced, preferably with sodium cyanoborohydride and acetic acid at 15°, to give the corresponding 4,5-dihydro compounds 10. These are alkylated on N_4 by

treatment with alkyl halide or dialkyl sulfate. Alternatively, the 4,5-dihydro compounds are acylated on N_4 by treatment with acyl halides or anhydrides, preferably in the presence of base such as triethylamine. The products are the alkyl and acyl derivatives 11. Alternatively, where R^1 is $-(CH_2)_mCOOR^6$ (R^6 not=H), 9 are treated with a base such as sodium hydroxide in methanol to give the acids 9 (R^1=$(CH_2)_mCOOH$).

The 3,5-disubstituted benzodiazepines 7 are treated with alkyl- or arylmagnesium halides, preferably methylmagnesium iodide, to give the dihydro compounds 12. The products are alkylated and acylated on nitrogen, as described for the 3,5-disubstituted-4,5-dihydro derivatives, to give the derivatives 13.

The 3,5-disubstituted benzodiazepines 7 are treated with P_2S_5 or Lawesson's reagent (2,4-bis-(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane) to give the 2-thiones 14. These are reduced with Raney nickel to the 2-unsubstituted compounds 15. The latter may be alkylated with alkyl halide or sulfate, acylated with acyl halide or anhydride, reduced with sodium cyanoborohydride, or substituted with alkyl- or aryl magnesium halide as described for 7 above.

Where the 3-position in a 3,5-disubstituted benzodiazepine 7 bears a substituent containing an indole moiety, preferably 3-indolylmethyl, reduction with triethylsilane/TFA provides the corresponding indoline 16. Alternatively, oxidation with HCl-dimethylsulfoxide provides the oxindole 17. 16 and 17 may be subjected to the reactions described for 7 to obtain alkyl, acyl, and dihydro derivatives.

Dialkyl, alkylacyl, and trialkyl compounds may also be made using these methods.

The 3,5-disubstituted benzodiazepines 7 may also be oxidized, preferably with m-chloroperoxybenzoic acid, to give the corresponding 4-N-oxides 7a.

Alternatively, (Scheme II) 3-unsubstituted-5-substituted-1-substituted or unsubstituted benzodiazepines 9 (R^1=H) (Scheme II) prepared as described in the prior art may be treated with base, preferably lithium diisopropylamide, in an inert solvent, preferably THF, according to the procedure of J. Org. Chem., 46 4945 (1981). The resulting salt may be alkylated to obtain 9 with, for example, benzyl bromide or gramine methiodide. The resulting racemates may be resolved to obtain the preferred 3(R) enantiomers, or may be used as such.

Alternatively, the salt may be treated with an alkyl or aryl aldehyde, ketone, or acid halide or anhydride to give the 1-hydroxymethylene compounds 9 (R^3=$\overset{OH}{\overset{|}{C}}HR^7$) or 9 ($R^3$=$\overset{OH}{\overset{|}{C}}R^7R^7_a$), the 1-ketomethylene derivatives 9 (R^3=$\overset{O}{\overset{\|}{C}}R^7$) and 32 ($R^3$=$\overset{O}{\overset{\|}{C}}R^7$). If the acid halide reaction is carried out in solvent containing peroxide, the 3- and 5-hydroxy analogs 20 and 21 (resp.) may be obtained.

The hydroxymethylene compounds 9 (R^3=$\overset{OH}{\overset{|}{C}}HR^7$) or ($R^3$=$\overset{OH}{\overset{|}{C}}R^7R^7_a$) may be treated with acids, preferably trifluoroacetic acid, to obtain the olefins 18, 19, and/or 22.

Alternatively, 3-substituted benzodiazepines 9 may be obtained by treating the 3-unsubstituted compound 9 (R^3=H) with 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) and alkylating agent such as alkyl halide or sulfate or, preferably, gramine methiodide. Resolution to obtain the preferred 3(R) enantiomer may be carried out as described above.

3-Amino-5-substituted-1-substituted or unsubstituted benzodiazepines 9 (R^3=NH_2) are prepared as described in the prior art. Alternatively, 9 (R^3=NH_2) are prepared as shown in Scheme IVb. Treatment of the 3-unsubstituted compound 9 (R^3=H) with a suitable base, preferably potassium t-butoxide, followed by a nitrosating agent, preferably isoamyl nitrate, provides the oxime 9 (R^3==NOH). Reduction, preferably with Raney nickel, gives the 3-amino compounds 9 (R^3=NH_2).

3-Amino and 3-aminomethyl-5-substituted-1-substituted or unsubstituted benzodiazepines 23 (Scheme III) are alkylated with alkyl halides or with α-halo acids and esters to give the alkyl derivatives 24 (R^3=$(CH_2)_n NH(CH_2)_q R^7$) and 9 (R^3=$(CH_2)_n$-$NHCH(CH_2)_q COOR^6$). With acyl halides, the amines 23 give the corresponding amides 24 (R^3=$(CH_2)_n NHC(=O)(CH_2)_q R^7$).

With isocyanates, the amines 23 give the corresponding ureas 24 (R^3=$(CH_2)_n NHC(=O)NH(CH_2)_q R^7$). With N-protected or unprotected α-amino acids and a coupling

reagent such as DCC, EDC, or isobutyl chloroformate, the amines 23 give the amides 24 ($R^3=(CH_2)_nNHC(=O)CH(NHCOOR^{14})CH_2R^7$).

3-Hydroxy-5-substituted-7-substituted or unsubstituted-1-substituted or unsubstituted benzodiazepines 24 (R^3=OH) (Scheme IIIb) are acylated with acyl halides to give the esters 24 ($R^3=OC(=O)(CH_2)_qR^7$).

3-Chloro-5-substituted-1-substituted or unsubstituted benzodiazepines 24 (R^3=Cl) (Scheme IV) may be used to monoalkylate amines to give the 3-substituted amino compounds 24 ($R^3=NH_2$). The 3-chloro compounds 29 may also be used to monoalkylate 1,2-ethanediamine and 1,3-propanediamine to give the compounds 24 ($R^3=NH(CH_2)NH_2$). These may be alkylated to provide 24 ($R^3=NH(CH_2)_nNH(CH_2)qR^7$) or acylated to give 24 ($R^3=NH(CH_2)_nNHC(=O)(CH_2)_qR^7$). Alternatively, the latter two compounds may be obtained from the previously mono-alkylated or acylated diamine and chloro compound 24 (R^3=Cl).

3-Substituted-5-substituted-7-substituted or unsubstituted benzodiazepines 24 (R^1=H) (Scheme IIIc) may be treated with sodium hydride in a suitable solvent, such as DMF, followed by an alkyl halide to provide the 1-alkyl derivatives 24. When an acrylate such as methyl or ethyl acrylate or acylonitrile is substituted for the alkyl halide, the 1-(2-substituted)ethyl compounds 24 (R^1=  Z) are obtained.

When R^3 contains R^7 where R^7 is 1-unsubstituted-2- or 3-indolyl (Scheme IIId), the compounds 24 may be further alkylated by treatment

with sodium hydride followed by an alkyl halide or an acrylate, such as methyl or ethyl acrylate or acrylonitrile, or an activated amino acid such as Boc-phenylalanine anhydride to give the corresponding 1-substituted indole compounds 24 (Scheme IIId) in which R^8 is as defined herein and R^8 is other than hydrogen.

The compounds 24 wherein R^1 and/or R^8 is $(CH_2)_m$-COOMe or $(CH_2)_m$-COOEt may be treated with sodium hydroxide in an aqueous solvent, preferably aqueous solvent, preferably aqueous methanol, and then acidified to give the corresponding acids 24, wherein R^1 and/or R^8 is $(CH_2)_nCOOH$. Alternatively, these same compounds may be treated with aqueous or anhydrous ammonia to give the amides 24 wherein R^1 and/or R^8 is $(CH_2)_mCONH_2$.

In cases where the starting materials are optically active, the chirality at C_3 is controlled by the synthesis. When racemic starting materials are employed, racemic products are obtained. The enantiomers may be separated by resolution.

In Vitro Activity of Formula I

The biological activity of the compounds of Formula I have been evaluated using 1.) an ^{125}I-CCK receptor binding assay and in vitro isolated tissue preparations and 2.) ^{125}I-gastrin and ^{3}H-pentagastrin binding assays.

Materials and Methods

1. CCK Receptor Binding (Pancreas)

CCK-33 was radiolabeled with ^{125}I-Bolton Hunter reagent (2000 Ci/mmole) as described by Sankara et al. (J. Biol. Chem. 254: 9349-9351, 1979). Receptor binding was performed according to Innis and Snyder (Proc. Natl. Acad. Sci. 77: 6917-6921, 1980) with the minor modification of adding the additional protease inhibitors, phenylmethane sulfonyl fluoride and o-phenanthroline. The latter two compounds have no effect on the ^{125}I-CCK receptor binding assay.

Male Sprague-Dawley rats (200-350g) were sacrificed by decapitation. The whole pancreas was dissected free of fat tissue and was homogenized in 20 volumes of ice-cold 50 mM, Tris HCl (pH 7.7 at 25°C) with a Brinkmann Polytron PT 10. The homogenates were centrifuged at 48,000 g for 10 min. Pellets were resuspended in Tris Buffer, centrifuged as above and resuspended in 200 volumes of binding assay buffer (50 mM Tris HCl, pH 7.7 at 25°C, 5 mM dithiothrietol, 0.1 mM bacitracin, 1.2 mM phenylmethane sulfonyl fluoride and 0.5 mM o-phenanthroline). For the binding assay, 25 µl of buffer (for total binding) or unlabeled CCK-8 sulfate to give a final concentration of 1 µM (for nonspecific binding) or the compounds of Formula I (for determination of inhibition of ^{125}I-CCK binding) and 25 µl of ^{125}I-CCK-33 (30,000-40,000 cpm) were added to 450 µl of the membrane suspensions in microfuge tubes. All assays were run in duplicate or triplicate. The reaction mixtures were incubated at 37°C for 30 minutes and centrifuged in a Beckman Microfuge (4

minutes) immediately after adding 1 ml of ice-cold incubation buffer. The supernatant was aspirated and discarded, pellets were counted with a Beckman gamma 5000. For Scatchard analysis (Ann. N.Y. Acad. Sci. 51: 660, 1949), ^{125}I-CCK-33 was progressively diluted with increasing concentrations of CCK-33.

2. CCK Receptor Binding (Brain)

CCK-33 was radiolabeled and the binding was performed according to the description for the pancreas method with modifications according to Saito et al., J. Neurochem. 37:483-490, 1981.

Male Hartley guinea pigs (300-500g) were sacrificed by decapitation and the brains were removed and placed in ice-cold 50 mM, Tris HCl plus 7.58 g/l Trizma-7.4 (pH 7.4 at 25°C). Cerebral cortex was dissected and used as a receptor source. Each gram of fresh guinea pig brain tissue was homogenized in 10 ml of Tris/Trizma buffer with a Brinkman polytron PT-10. The homogenates were centrifuged at 42,000 g for 15 minutes. Pellets were resuspended in Tris Buffer, centrifuged as above and resuspended in 200 volumes of binding assay buffer (10 mM N-2-hydroxyethyl-piperazine-N'-2-ethane sulfonic acid (HEPES), 5 mM $MgCl_2$, 0.25 mg/ml bacitracin, 1 mM ethylene glycol-bis-(ß-aminoethyl-ether-N,N'-tetraacetic acid) (EGTA), and 0.4% bovine serum albumin (BSA)). For the binding assay, 25 µl of buffer (for total binding) or unlabeled CCK-8 sulfate to give a final concentration of 1µm (for nonspecific binding) or the compounds of Formula I (for determination of inhibition of ^{125}I-CCK binding) and 25 µl of ^{125}I-CCK-33 (30,000-40,000

cpm) were added to 450 µl of the membrane suspensions in microfuge tubes. All assays were run in duplicate or triplicate. The reaction mixtures were incubated at 25°C for 2 hours and centrifuged in a Beckman Microfuge (4 minutes) immediately after adding 1 ml of ice-cold incubation buffer. The supernatant was aspirated and discarded, pellets were counted with a Beckman gamma 5000.

The compounds of Formula I can be determined to be competitive antagonists of CCK according to the following assays.

3. Isolated guinea pig gall bladder

Male Hartley guinea pigs (400-600 g) are sacrificed by decapitation. The whole gall bladder is dissected free from adjacent tissues and cut into two equal halves. The gall bladder strips are suspended along the axis of the bile duct in a 5 ml organ bath under 1 g tension. The organ bath contains a Kreb's bicarbonate solution (NaCl 118 mM, KCl 4.75 mM, CaCl 2.54 mM, KH_2PO_4 1.19 mM, Mg SO_4 1.2 mM, $NaHCO_3$ 25 mM and dextrose 11 mM) maintained at 32°C and bubbled with 95% O_2 and 5% CO_2. Isometric contractions are recorded using Statham (60 g; 0.12 mm) strain gauges and a Hewlett-Packard (77588) recorder. The tissues are washed every 10 minutes for 1 hour to obtain equilibrium prior to the beginning of the study. CCK-8 is added cumulatively to the baths and EC_{50}'s determined using regression analysis. After washout (every 10 minutes for 1 hour), the compound of Formula I is added at least 5 minutes before the

addition of CCk-8 and the EC_{50} of CCK-8 in the presence of the compound of Formula I similarly determined.

4. Isolated longitudinal muscle of guinea pig ileum

Longitudinal muscle strips with attached nerve plexus are prepared as described in Brit. J. Pharmac. 23: ; 356-363, 1964; J. Physiol. 194: 13-33, 1969. Male Hartley guinea pigs are decapitated and the ileum removed (10 cm of the terminal ileum is discarded and the adjacent 20 cm piece used). A piece (10 cm) of the ileum is stretched on a glass pipette. Using a cotton applicator to stroke tangentially away from the mesentery attachment at one end, the longitudinal muscle is separated from the underlying circular muscle. The longitudinal muscle is then tied to a thread and by gently pulling, stripped away from the entire muscle. A piece of approximately 2 cm is suspended in 5 ml organ bath containing Krebs solution and bubbled with 95% O_2 and 5% CO_2 at 37°C under 0.5 g tension. CCK-8 is added cumulatively to the baths and EC_{50} values in the presence and absence of compounds of Formula I determined as described in the gall bladder protocol (above).

Gastrin Antagonism

Gastrin antagonist activity of compounds of Formula I is determined using the following assay.

Gastrin Receptor Binding in Guinea Pig Gastric Glands

Preparation of guinea pig gastric mucosal glands

Guinea pig gastric mucosal glands were prepared by the procedure of Berglingh and Obrink Acta Physiol. Scand. 96: 150 (1976) with a slight modification according to Praissman et al. C. J. Receptor Res. 3: (1983). Gastric mucosa from guinea pigs (300-500 g body weight, male Hartley) were washed thoroughly and minced with fine scissors in standard buffer consisting of the following: 130 mM NaCl, 12 mM $NaHCO_3$, 3 mM NaH_2PO_4, 3 mM Na_2HPO_4, 3 mM K_2HPO_4, 2 mM $MgSO_4$, 1mM $CaCl_2$, 5 mM glucose and 4 mM L-glutamine, 25 mM HEPES at pH 7.4. The minced tissues were washed and then incubated in a 37°C shaker bath for 40 minutes with the buffer containing 0.1% collagenase and 0.1% BSA and bubbled with 95% O_2 and 5% CO_2. The tissues were passed twice through a 5 ml glass syringe to liberate the gastric glands, and then filtered through 200 mesh nylon. The filtered glands were centrifuged at 270 g for 5 minutes and washed twice by resuspension and centrifugation.

Binding studies

The washed guinea pig gastric glands prepared as above were resuspended in 25 ml of standard buffer containing 0.25 mg/ml of bacitracin. For binding studies, to 220 µl of gastric glands in triplicate tubes, 10 µl of buffer (for total binding) or gastrin (1 µM final concentration, for nonspecific binding) or test compound and 10 µl of ^{125}I-gastrin (NEN, 2200 Ci/mmole, 25 pM final) or ^{3}H-pentagastrin (NEN 22 Ci/mmole, 1 nM final) were added. The tubes

were aerated with 95% O_2 and 5% CO_2 and capped. The reaction mixtures after incubation at 25°C for 30 minutes were filtered under reduced pressure on glass G/F B filters (Whatman) and immediately washed further with 4 x 4 ml of standard buffer containing 0.1% BSA. The radioactivity on the filters was measured using a Beckman gamma 5500 for ^{125}I-gastrin or liquid scintillation counting for ^{3}H-pentagastrin.

In Vitro Results

1. Effect of The Compounds of Formula I on ^{125}I-CCK-33 receptor binding

The preferred compounds of Formula I are those which inhibited specific ^{125}I-CCK-33 binding in a concentration dependent manner.

Scatchard analysis of specific ^{125}I-CCK-33 receptor binding in the absence and presence of the compounds of Formula I indicated the compound of Formula I competitively inhibited specific ^{125}I-CCK-33 receptor binding since it increased the K_D (dissociation constant) without affecting the B_{max} (maximum receptor number). A K_i value (dissociation constant of inhibitor) of the compounds of Formula I was estimated.

The data of Table I were obtained for compounds of Formula I.

TABLE I

CCK Receptor Binding Results

Compound of Example	IC_{50} (μM) ^{125}I-CCK Pancreas	^{125}I-CCK Brain
2 & 3	0.40	81.50
4a & 44	0.36	16.00
4b	0.27	18.00
5	3.40	100.00
6	1.20	50.00
12	4.00	ca. 100
28	5.00	ca. 100
31	1.40	ca. 100
34	4.50	ca. 100
36	0.30	30.00
37	2.20	30.00
39	100.00	30.00
40	3.60	ca. 100
43	0.30	23.00
50	15.00	2.60
51	ca. 100	32
52	ca. 100	33
53a	100.00	2.60
57	2.90	100.00
58	18.00	12.00
59	1.40	ca. 100
60	1.30	100.00
68	7.00	30.00
73	0.0047	8.00
74	3.00	100.00

TABLE I (cont'd)
CCK Receptor Binding Results

Compound of Example	IC_{50} (μM) ^{125}I-CCK Pancreas	^{125}I-CCK Brain
75	4.80	100.00
76	1.00	11.00
77	6.00	20.00
78	0.0014	6
79(A)	0.0008	0.8
79(B)	0.0014	15
80	0.0023	3.4
81a	0.0014	0.3
81b	0.0013	1.0
87	0.0011	0.27
88	0.0006	0.3
89	0.019	1.1
90	0.049	11
91	0.0025	2.9
92	0.0043	1.6
93	0.7	2.9
94	0.053	3.8
105	0.0021	3
111	0.006	40
113	0.0015	5.6
114	0.005	12
121	0.011	5.5
I28	0.009	32
131	0.0083	40

TABLE I (cont'd)
CCK Receptor Binding Results

Compound of Example	IC_{50} (μM) ^{125}I-CCK Pancreas	^{125}I-CCK Brain
132	0.032	>100
134	0.015	40
154	0.0035	3.5
156	0.0035	4
159	0.0034	3
160	0.020	12
167	0.00075	1.7
168	0.015	2.4

Preferred compounds of Formula I are those wherein R' is H, methyl, ethyl, carboxymethyl, ethyl-carboxymethyl and carboxyethyl.

Other series of preferred compounds are those wherein R^2 is phenyl, p-chlorophenyl, o-chlorophenyl, p-fluorophenyl, o-fluorophenyl, 2-4-dichlorophenyl, 2-6-difluorophenyl, $-CH_2COO$-t-butyl, or $-CH_2COOEt$.

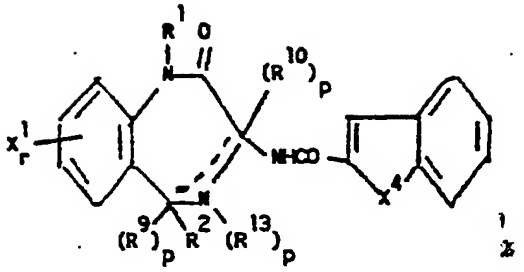
Other series of preferred compounds are those wherein R^3 is 2- or 3-indolylmethyl, -CO-thiophene, -NHCO-2-indolyl, NHCO-2-(1-methyl-indolyl), NHCO-2-(5-fluoroindolyl), NHCO-2-benzo-furanyl, NHCO-2-benzothieyl, NHCO-2-(3-methyl-indenyl), NHCO-(mono- or dihalophenyl), NHCO-phenyl-ethenyl, NHCO-(mono- or dimethyl or trifluoro-methylphenyl), NHCONH-(mono- or di-halophenyl), CO-2-(1-methyl)-indolyl, CO-3-(1-methyl)indolyl, or -CHOH-1-methylindol-3-yl.

When p is 1 for any of R^9, R^{10}, or R^{13}, it is preferred that R^9 is H or hydroxyl, R^{10} is H or hydroxyl, and R^{13} is H.

It is preferred that X^1_r is H, Cl, F, CF_3, OH or NO_2.

Examples of Formula I compounds are tabulated below.

TABLE 2



X^4=NH, N-CH_3, O, or S

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
H	1	H	-	Ph	-	H
Cl	1	H	-	Ph	-	H
F	1	H	-	Ph	-	H
CF_3	1	H	-	Ph	-	H
OH	1	H	-	Ph	-	H
NO_2	1	H	-	Ph	-	H
H	1	CH_3	-	Ph	-	H
Cl	1	CH_3	-	Ph	-	H
F	1	CH_3	-	Ph	-	H
CF_3	1	CH_3	-	Ph	-	H
OH	1	CH_3	-	Ph	-	H
NO_2	1	CH_3	-	Ph	-	H
H	1	CH_2COOH	-	Ph	-	H
Cl	1	CH_2COOH	-	Ph	-	H
F	1	CH_2COOH	-	Ph	-	H
CF_3	1	CH_2COOH	-	Ph	-	H
OH	1	CH_2COOH	-	Ph	-	H
NO_2	1	CH_2COOH	-	Ph	-	H
H	1	CH_2CH_3	-	Ph	-	H
OH	1	CH_2CH_3	-	Ph	-	H
H	1	CH_2COOEt	-	Ph	-	H
OH	1	CH_2COOEt	-	Ph	-	H
H	1	CH_2CH_2COOH	-	Ph	-	H

TABLE 2 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
OH	1	CH_2CH_2COOH	-	Ph	-	H
H	1	H	-	o-F-Ph	-	H
Cl	1	H	-	o-F-Ph	-	H
F	1	H	-	o-F-Ph	-	H
CF_3	1	H	-	o-F-Ph	-	H
OH	1	H	-	o-F-Ph	-	H
NO_2	1	H	-	o-F-Ph	-	H
H	1	CH_3	-	o-F-Ph	-	H
Cl	1	CH_3	-	o-F-Ph	-	H
F	1	CH_3	-	o-F-Ph	-	H
CF_3	1	CH_3	-	o-F-Ph	-	H
OH	1	CH_3	-	o-F-Ph	-	H
NO_2	1	CH_3	-	o-F-Ph	-	H
H	1	CH_2COOH	-	o-F-Ph	-	H
Cl	1	CH_2COOH	-	o-F-Ph	-	H
F	1	CH_2COOH	-	o-F-Ph	-	H
CF_3	1	CH_2COOH	-	o-F-Ph	-	H
OH	1	CH_2COOH	-	o-F-Ph	-	H
NO_2	1	CH_2COOH	-	o-F-Ph	-	H
H	1	CH_2CH_3	-	o-F-Ph	-	H
OH	1	CH_2CH_3	-	o-F-Ph	-	H
H	1	CH_2COOEt	-	o-F-Ph	-	H
OH	1	CH_2COOEt	-	o-F-Ph	-	H
H	1	CH_2CH_2COOH	-	o-F-Ph	-	H
OH	1	CH_2CH_2COOH	-	o-F-Ph	-	H
H	1	H	-	p-Cl-Ph	-	H
F	1	H	-	p-Cl-Ph	-	H
CF_3	1	H	-	p-Cl-Ph	-	H
OH	1	H	-	p-Cl-Ph	-	H
H	1	CH_3	-	p-Cl-Ph	-	H

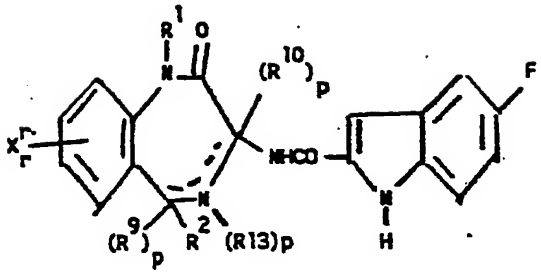
TABLE 2 (cont'd)

R^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
F	1	CH_3	-	p-Cl-Ph	-	H
CF_3	1	CH_3	-	p-Cl-Ph	-	H
OH	1	CH_3	-	p-Cl-Ph	-	H
H	1	CH_2COOH	-	p-Cl-Ph	-	H
F	1	CH_2COOH	-	p-Cl-Ph	-	H
CF_3	1	CH_2COOH	-	p-Cl-Ph	-	H
OH	1	CH_2COOH	-	p-Cl-Ph	-	H
H	1	CH_2CH_3	-	p-Cl-Ph	-	H
H	1	CH_2COOEt	-	p-Cl-Ph	-	H
H	1	CH_2CH_2COOH	-	p-Cl-Ph	-	H
H	1	H	-	CH_2COOt-Bu	-	H
Cl	1	H	-	CH_2COOt-Bu	-	H
F	1	H	-	CH_2COOt-Bu	-	H
CF_3	1	H	-	CH_2COOt-Bu	-	H
OH	1	H	-	CH_2COOt-Bu	-	H
NO_2	1	H	-	CH_2COOt-Bu	-	H
H	1	CH_3	-	CH_2COOt-Bu	-	H
Cl	1	CH_3	-	CH_2COOt-Bu	-	H
F	1	CH_3	-	CH_2COOt-Bu	-	H
CF_3	1	CH_3	-	CH_2COOt-Bu	-	H
OH	1	CH_3	-	CH_2COOt-Bu	-	H
NO_2	1	CH_3	-	CH_2COOt-Bu	-	H
H	1	CH_2COOH	-	CH_2COOt-Bu	-	H
Cl	1	CH_2COOH	-	CH_2COOt-Bu	-	H
F	1	CH_2COOH	-	CH_2COOt-Bu	-	H
CF_3	1	CH_2COOH	-	CH_2COOt-Bu	-	H
OH	1	CH_2COOH	-	CH_2COOt-Bu	-	H
NO_2	1	CH_2COOH	-	CH_2COOt-Bu	-	H
H	1	CH_2CH_3	-	CH_2COOt-Bu	-	H
OH	1	CH_2CH_3	-	CH_2COOt-Bu	-	H

TABLE 2 (cont'd)

	X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
5	H	1	CH_2COOEt	-	$CH_2COOt\text{-}Bu$	-	H
	OH	1	CH_2COOEt	-	$CH_2COOt\text{-}Bu$	-	
	H	1	CH_2CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
	OH	1	CH_2CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
	H	1	H	-	CH_2COOEt	-	H
10	Cl	1	H	-	CH_2COOEt	-	H
	F	1	H	-	CH_2COOEt	-	H
	CF_3	1	H	-	CH_2COOEt	-	H
	OH	1	H	-	CH_2COOEt	-	H
	NO_2	1	H	-	CH_2COOEt	-	H
15	H	1	CH_3	-	CH_2COOEt	-	H
	Cl	1	CH_3	-	CH_2COOEt	-	H
	F	1	CH_3	-	CH_2COOEt	-	H
	CF_3	1	CH_3	-	CH_2COOEt	-	H
	OH	1	CH_3	-	CH_2COOEt	-	H
20	NO_2	1	CH_3	-	CH_2COOEt	-	H
	H	1	CH_2COOH	-	CH_2COOEt	-	H
	Cl	1	CH_2COOH	-	CH_2COOEt	-	H
	F	1	CH_2COOH	-	CH_2COOEt	-	H
	CF_3	1	CH_2COOH	-	CH_2COOEt	-	H
25	OH	1	CH_2COOH	-	CH_2COOEt	-	H
	NO_2	1	CH_2COOH	-	CH_2COOEt	-	H
	H	1	CH_2CH_3	-	CH_2COOEt	-	H
	OH	1	CH_2CH_3	-	CH_2COOEt	-	H
	H	1	CH_2COOEt	-	CH_2COOEt	-	H
30	OH	1	CH_2COOEt	-	CH_2COOEt	-	H
	H	1	CH_2CH_2COOH	-	CH_2COOEt	-	
	OH	1	CH_2CH_2COOH	-	CH_2COOEt	-	

TABLE 3



X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
H	1	H	-	Ph	-	H
Cl	1	H	-	Ph	-	H
F	1	H	-	Ph	-	H
CF_3	1	H	-	Ph	-	H
OH	1	H	-	Ph	-	H
NO_2	1	H	-	Ph	-	H
H	1	CH_3	-	Ph	-	H
Cl	1	CH_3	-	Ph	-	H
F	1	CH_3	-	Ph	-	H
CF_3	1	CH_3	-	Ph	-	H
OH	1	CH_3	-	Ph	-	H
NO_2	1	CH_3	-	Ph	-	H
H	1	CH_2COOH	-	Ph	-	H
Cl	1	CH_2COOH	-	Ph	-	H
F	1	CH_2COOH	-	Ph	-	H
CF_3	1	CH_2COOH	-	Ph	-	H
OH	1	CH_2COOH	-	Ph	-	H
NO_2	1	CH_2COOH	-	Ph	-	H
H	1	CH_2CH_3	-	Ph	-	H
OH	1	CH_2CH_3	-	Ph	-	H

TABLE 3 (cont'd)

	X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
	H	1	CH_2COOEt	-	Ph	-	H
	OH	1	CH_2COOEt	-	Ph	-	H
	H	1	CH_2CH_2COOH	-	Ph	-	H
	OH	1	CH_2CH_2COOH	-	Ph	-	H
	H	1	H	-	o-F-Ph	-	H
	Cl	1	H	-	o-F-Ph	-	H
	F	1	H	-	o-F-Ph	-	H
	CF_3	1	H	-	o-F-Ph	-	H
	OH	1	H	-	o-F-Ph	-	H
	NO_2	1	H	-	o-F-Ph	-	H
	H	1	CH_3	-	o-F-Ph	-	H
	Cl	1	CH_3	-	o-F-Ph	-	H
	F	1	CH_3	-	o-F-Ph	-	H
	CF_3	1	CH_3	-	o-F-Ph	-	H
	OH	1	CH_3	-	o-F-Ph	-	H
	NO_2	1	CH_3	-	o-F-Ph	-	H
	H	1	CH_2COOH	-	o-F-Ph	-	H
	Cl	1	CH_2COOH	-	o-F-Ph	-	H
	F	1	CH_2COOH	-	o-F-Ph	-	H
	CF_3	1	CH_2COOH	-	o-F-Ph	-	H
	OH	1	CH_2COOH	-	o-F-Ph	-	H
	NO_2	1	CH_2COOH	-	o-F-Ph	-	H
	H	1	CH_2CH_3	-	o-F-Ph	-	H
	OH	1	CH_2CH_3	-	o-F-Ph	-	H
	H	1	CH_2COOEt	-	o-F-Ph	-	H
	OH	1	CH_2COOEt	-	o-F-Ph	-	H
	H	1	CH_2CH_2COOH	-	o-F-Ph	-	H
	OH	1	CH_2CH_2COOH	-	o-F-Ph	-	H
	H	1	H	-	p-Cl-Ph	-	H
	F	1	H	-	p-Cl-Ph	-	H

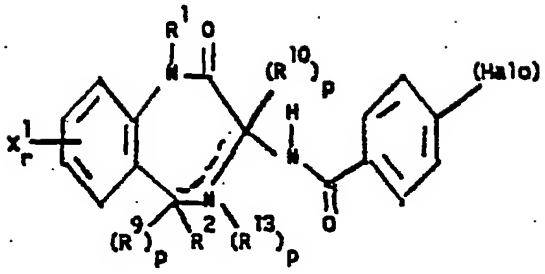
TABLE 3 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
CF_3	1	H	-	p-Cl-Ph	-	H
OH	1	H	-	p-Cl-Ph	-	H
H	1	CH_3	-	p-Cl-Ph	-	H
F	1	CH_3	-	p-Cl-Ph	-	H
CF_3	1	CH_3	-	p-Cl-Ph	-	H
OH	1	CH_3	-	p-Cl-Ph	-	H
H	1	CH_2COOH	-	p-Cl-Ph	-	H
F	1	CH_2COOH	-	p-Cl-Ph	-	H
CF_3	1	CH_2COOH	-	p-Cl-Ph	-	H
OH	1	CH_2COOH	-	p-Cl-Ph	-	H
H	1	CH_2CH_3	-	p-Cl-Ph	-	H
H	1	CH_2COOEt	-	p-Cl-Ph	-	H
H	1	CH_2CH_2COOH	-	p-Cl-Ph	-	H
H	1	H	-	CH_2COOt-Bu	-	H
Cl	1	H	-	CH_2COOt-Bu	-	H
F	1	H	-	CH_2COOt-Bu	-	H
CF_3	1	H	-	CH_2COOt-Bu	-	H
OH	1	H	-	CH_2COOt-Bu	-	H
NO_2	1	H	-	CH_2COOt-Bu	-	H
H	1	CH_3	-	CH_2COOt-Bu	-	H
Cl	1	CH_3	-	CH_2COOt-Bu	-	H
F	1	CH_3	-	CH_2COOt-Bu	-	H
CF_3	1	CH_3	-	CH_2COOt-Bu	-	H
OH	1	CH_3	-	CH_2COOt-Bu	-	H
NO_2	1	CH_3	-	CH_2COOt-Bu	-	H
H	1	CH_2COOH	-	CH_2COOt-Bu	-	H
Cl	1	CH_2COOH	-	CH_2COOt-Bu	-	H
F	1	CH_2COOH	-	CH_2COOt-Bu	-	H
CF_3	1	CH_2COOH	-	CH_2COOt-Bu	-	H
OH	1	CH_2COOH	-	CH_2COOt-Bu	-	H

TABLE 3 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
NO_2	1	CH_2COOH	-	CH_2COOt-Bu	-	H
H	1	CH_2CH_3	-	CH_2COOt-Bu	-	H
OH	1	CH_2CH_3	-	CH_2COOt-Bu	-	H
H	1	CH_2COOEt	-	CH_2COOt-Bu	-	H
OH	1	CH_2COOEt	-	CH_2COOt-Bu	-	H
H	1	CH_2CH_2COOH	-	CH_2COOt-Bu	-	H
OH	1	CH_2CH_2COOH	-	CH_2COOt-Bu	-	H
H	1	H	-	CH_2COOEt	-	H
Cl	1	H	-	CH_2COOEt	-	H
F	1	H	-	CH_2COOEt	-	H
CF_3	1	H	-	CH_2COOEt	-	H
OH	1	H	-	CH_2COOEt	-	H
NO_2	1	H	-	CH_2COOEt	-	H
H	1	CH_3	-	CH_2COOEt	-	H
Cl	1	CH_3	-	CH_2COOEt	-	H
F	1	CH_3	-	CH_2COOEt	-	H
CF_3	1	CH_3	-	CH_2COOEt	-	H
OH	1	CH_3	-	CH_2COOEt	-	H
NO_2	1	CH_3	-	CH_2COOEt	-	H
H	1	CH_2COOH	-	CH_2COOEt	-	H
Cl	1	CH_2COOH	-	CH_2COOEt	-	H
F	1	CH_2COOH	-	CH_2COOEt	-	H
CF_3	1	CH_2COOH	-	CH_2COOEt	-	H
OH	1	CH_2COOH	-	CH_2COOEt	-	H
NO_2	1	CH_2COOH	-	CH_2COOEt	-	H
H	1	CH_2CH_3	-	CH_2COOEt	-	H
OH	1	CH_2CH_3	-	CH_2COOEt	-	H
H	1	CH_2COOEt	-	CH_2COOEt	-	H
OH	1	CH_2COOEt	-	CH_2COOEt	-	H
H	1	CH_2CH_2COOH	-	CH_2COOEt	-	H
OH	1	CH_2CH_2COOH	-	CH_2COOEt	-	H

TABLE 4



X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
H	1	H	-	Ph	-	H
Cl	1	H	-	Ph	-	H
F	1	H	-	Ph	-	H
CF_3	1	H	-	Ph	-	H
OH	1	H	-	Ph	-	H
NO_2	1	H	-	Ph	-	H
H	1	CH_3	-	Ph	-	H
Cl	1	CH_3	-	Ph	-	H
F	1	CH_3	-	Ph	-	H
CF_3	1	CH_3	-	Ph	-	H
OH	1	CH_3	-	Ph	-	H
NO_2	1	CH_3	-	Ph	-	H
H	1	CH_2COOH	-	Ph	-	H
Cl	1	CH_2COOH	-	Ph	-	H
F	1	CH_2COOH	-	Ph	-	H
CF_3	1	CH_2COOH	-	Ph	-	H
OH	1	CH_2COOH	-	Ph	-	H
NO_2	1	CH_2COOH	-	Ph	-	H
H	1	CH_2CH_3	-	Ph	-	H
OH	1	CH_2CH_3	-	Ph	-	H

TABLE 4 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
H	1	CH_2COOEt	-	Ph	-	H
OH	1	CH_2COOEt	-	Ph	-	H
H	1	CH_2CH_2COOH	-	Ph	-	H
OH	1	CH_2CH_2COOH	-	Ph	-	H
H	1	H	-	o-F-Ph	-	H
Cl	1	H	-	o-F-Ph	-	H
F	1	H	-	o-F-Ph	-	H
CF_3	1	H	-	o-F-Ph	-	H
OH	1	H	-	o-F-Ph	-	H
NO_2	1	H	-	o-F-Ph	-	H
H	1	CH_3	-	o-F-Ph	-	H
Cl	1	CH_3	-	o-F-Ph	-	H
F	1	CH_3	-	o-F-Ph	-	H
CF_3	1	CH_3	-	o-F-Ph	-	H
OH	1	CH_3	-	o-F-Ph	-	H
NO_2	1	CH_3	-	o-F-Ph	-	H
H	1	CH_2COOH	-	o-F-Ph	-	H
Cl	1	CH_2COOH	-	o-F-Ph	-	H
F	1	CH_2COOH	-	o-F-Ph	-	H
CF_3	1	CH_2COOH	-	o-F-Ph	-	H
OH	1	CH_2COOH	-	o-F-Ph	-	H
NO_2	1	CH_2COOH	-	o-F-Ph	-	H
H	1	CH_2CH_3	-	o-F-Ph	-	H
OH	1	CH_2CH_3	-	o-F-Ph	-	H
H	1	CH_2COOEt	-	o-F-Ph	-	H
OH	1	CH_2COOEt	-	o-F-Ph	-	H
H	1	CH_2CH_2COOH	-	o-F-Ph	-	H
OH	1	CH_2CH_2COOH	-	o-F-Ph	-	H
H	1	H	-	p-Cl-Ph	-	H
F	1	H	-	p-Cl-Ph	-	H

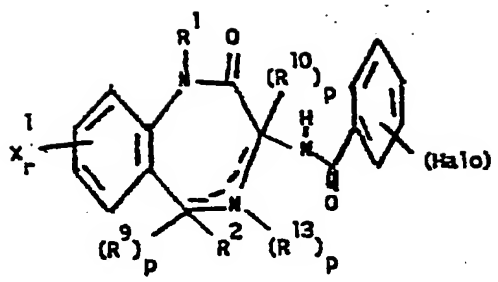
TABLE 4 (cont'd)

	X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
5	CF_3	1	H	-	p-Cl-Ph	-	H
	OH	1	H	-	p-Cl-Ph	-	H
	H	1	CH_3	-	p-Cl-Ph	-	H
	F	1	CH_3	-	p-Cl-Ph	-	H
	CF_3	1	CH_3	-	p-Cl-Ph	-	H
10	OH	1	CH_3	-	p-Cl-Ph	-	H
	H	1	CH_2COOH	-	p-Cl-Ph	-	H
	F	1	CH_2COOH	-	p-Cl-Ph	-	H
	CF_3	1	CH_2COOH	-	p-Cl-Ph	-	H
	OH	1	CH_2COOH	-	p-Cl-Ph	-	H
15	H	1	CH_2CH_3	-	p-Cl-Ph	-	H
	H	1	CH_2COOEt	-	p-Cl-Ph	-	H
	H	1	CH_2CH_2COOH	-	p-Cl-Ph	-	H
	H	1	H	-	CH_2COOt-Bu	-	H
	Cl	1	H	-	CH_2COOt-Bu	-	H
20	F	1	H	-	CH_2COOt-Bu	-	H
	CF_3	1	H	-	CH_2COOt-Bu	-	H
	OH	1	H	-	CH_2COOt-Bu	-	H
	NO_2	1	H	-	CH_2COOt-Bu	-	H
	H	1	CH_3	-	CH_2COOt-Bu	-	H
25	Cl	1	CH_3	-	CH_2COOt-Bu	-	H
	F	1	CH_3	-	CH_2COOt-Bu	-	H
	CF_3	1	CH_3	-	CH_2COOt-Bu	-	H
	OH	1	CH_3	-	CH_2COOt-Bu	-	H
	NO_2	1	CH_3	-	CH_2COOt-Bu	-	H
30	H	1	CH_2COOH	-	CH_2COOt-Bu	-	H
	Cl	1	CH_2COOH	-	CH_2COOt-Bu	-	H
	F	1	CH_2COOH	-	CH_2COOt-Bu	-	H
	CF_3	1	CH_2COOH	-	CH_2COOt-Bu	-	H
	OH	1	CH_2COOH	-	CH_2COOt-Bu	-	H

TABLE 4 (cont'd)

	X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
	NO_2	1	CH_2COOH	-	CH_2COOt-Bu	-	H
	H	1	CH_2CH_3	-	CH_2COOt-Bu	-	H
	OH	1	CH_2CH_3	-	CH_2COOt-Bu	-	H
	H	1	CH_2COOEt	-	CH_2COOt-Bu	-	H
	OH	1	CH_2COOEt	-	CH_2COOt-Bu	-	H
	H	1	CH_2CH_2COOH	-	CH_2COOt-Bu	-	H
	OH	1	CH_2CH_2COOH	-	CH_2COOt-Bu	-	H
	H	1	H	-	CH_2COOEt	-	H
	Cl	1	H	-	CH_2COOEt	-	H
	F	1	H	-	CH_2COOEt	-	H
	CF_3	1	H	-	CH_2COOEt	-	H
	OH	1	H	-	CH_2COOEt	-	H
	NO_2	1	H	-	CH_2COOEt	-	H
	H	1	CH_3	-	CH_2COOEt	-	H
	Cl	1	CH_3	-	CH_2COOEt	-	H
	F	1	CH_3	-	CH_2COOEt	-	H
	CF_3	1	CH_3	-	CH_2COOEt	-	H
	OH	1	CH_3	-	CH_2COOEt	-	H
	NO_2	1	CH_3	-	CH_2COOEt	-	H
	H	1	CH_2COOH	-	CH_2COOEt	-	H
	Cl	1	CH_2COOH	-	CH_2COOEt	-	H
	F	1	CH_2COOH	-	CH_2COOEt	-	H
	CF_3	1	CH_2COOH	-	CH_2COOEt	-	H
	OH	1	CH_2COOH	-	CH_2COOEt	-	H
	NO_2	1	CH_2COOH	-	CH_2COOEt	-	H
	H	1	CH_2CH_3	-	CH_2COOEt	-	H
	OH	1	CH_2CH_3	-	CH_2COOEt	-	H
	H	1	CH_2COOEt	-	CH_2COOEt	-	H
	OH	1	CH_2COOEt	-	CH_2COOEt	-	H
	H	1	CH_2CH_2COOH	-	CH_2COOEt	-	H
	OH	1	CH_2CH_2COOH	-	CH_2COOEt	-	H

TABLE 5



X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
H	1	H	-	Ph	-	H
Cl	1	H	-	Ph	-	H
F	1	H	-	Ph	-	H
CF_3	1	H	-	Ph	-	H
OH	1	H	-	Ph	-	H
NO_2	1	H	-	Ph	-	H
H	1	CH_3	-	Ph	-	H
Cl	1	CH_3	-	Ph	-	H
F	1	CH_3	-	Ph	-	H
CF_3	1	CH_3	-	Ph	-	H
OH	1	CH_3	-	Ph	-	H
NO_2	1	CH_3	-	Ph	-	H
H	1	CH_2COOH	-	Ph	-	H
Cl	1	CH_2COOH	-	Ph	-	H
F	1	CH_2COOH	-	Ph	-	H
CF_3	1	CH_2COOH	-	Ph	-	H
OH	1	CH_2COOH	-	Ph	-	H
NO_2	1	CH_2COOH	-	Ph	-	H
H	1	CH_2CH_3	-	Ph	-	H

TABLE 5 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
OH	1	CH_2CH_3	-	Ph	-	H
H	1	CH_2COOEt	-	Ph	-	H
OH	1	CH_2COOEt	-	Ph	-	H
H	1	CH_2CH_2COOH	-	Ph	-	H
OH	1	CH_2CH_2COOH	-	Ph	-	H
H	1	H	-	o-F-Ph	-	H
Cl	1	H	-	o-F-Ph	-	H
F	1	H	-	o-F-Ph	-	H
CF_3	1	H	-	o-F-Ph	-	H
OH	1	H	-	o-F-Ph	-	H
NO_2	1	H	-	o-F-Ph	-	H
H	1	CH_3	-	o-F-Ph	-	H
Cl	1	CH_3	-	o-F-Ph	-	H
F	1	CH_3	-	o-F-Ph	-	H
CF_3	1	CH_3	-	o-F-Ph	-	H
OH	1	CH_3	-	o-F-Ph	-	H
NO_2	1	CH_3	-	o-F-Ph	-	H
H	1	CH_2COOH	-	o-F-Ph	-	H
Cl	1	CH_2COOH	-	o-F-Ph	-	H
F	1	CH_2COOH	-	o-F-Ph	-	H
CF_3	1	CH_2COOH	-	o-F-Ph	-	H
OH	1	CH_2COOH	-	o-F-Ph	-	H
NO_2	1	CH_2COOH	-	o-F-Ph	-	H
H	1	CH_2CH_3	-	o-F-Ph	-	H
OH	1	CH_2CH_3	-	o-F-Ph	-	H
H	1	CH_2COOEt	-	o-F-Ph	-	H
OH	1	CH_2COOEt	-	o-F-Ph	-	H
H	1	CH_2CH_2COOH	-	o-F-Ph	-	H
OH	1	CH_2CH_2COOH	-	o-F-Ph	-	H

TABLE 5 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
H	1	H	-	o-Cl-Ph	-	H
F	1	H	-	p-Cl-Ph	-	H
CF_3	1	H	-	p-Cl-Ph	-	H
OH	1	H	-	p-Cl-Ph	-	H
H	1	CH_3	-	p-Cl-Ph	-	H
F	1	CH_3	-	p-Cl-Ph	-	H
CF_3	1	CH_3	-	p-Cl-Ph	-	H
OH	1	CH_3	-	p-Cl-Ph	-	H
H	1	CH_2COOH	-	p-Cl-Ph	-	H
F	1	CH_2COOH	-	p-Cl-Ph	-	H
CF_3	1	CH_2COOH	-	p-Cl-Ph	-	H
OH	1	CH_2COOH	-	p-Cl-Ph	-	H
H	1	CH_2CH_3	-	p-Cl-Ph	-	H
H	1	CH_2COOEt	-	p-Cl-Ph	-	H
H	1	CH_2CH_2COOH	-	p-Cl-Ph	-	H
H	1	H	-	CH_2COOt-Bu	-	H
Cl	1	H	-	CH_2COOt-Bu	-	H
F	1	H	-	CH_2COOt-Bu	-	H
CF_3	1	H	-	CH_2COOt-Bu	-	H
OH	1	H	-	CH_2COOt-Bu	-	H
NO_2	1	H	-	CH_2COOt-Bu	-	H
H	1	CH_3	-	CH_2COOt-Bu	-	H
Cl	1	CH_3	-	CH_2COOt-Bu	-	H
F	1	CH_3	-	CH_2COOt-Bu	-	H
CF_3	1	CH_3	-	CH_2COOt-Bu	-	H
OH	1	CH_3	-	CH_2COOt-Bu	-	H
NO_2	1	CH_3	-	CH_2COOt-Bu	-	H
H	1	CH_2COOH	-	CH_2COOt-Bu	-	H
Cl	1	CH_2COOH	-	CH_2COOt-Bu	-	H
F	1	CH_2COOH	-	CH_2COOt-Bu	-	H

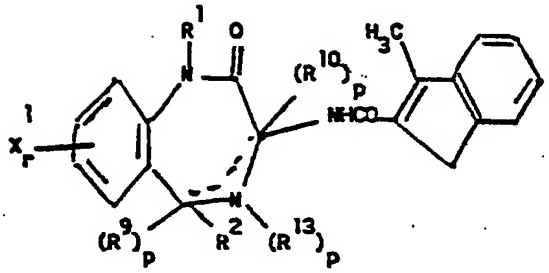
TABLE 5 (cont'd)

X^1	r	R^1		$(R^9)_p$	R^2		$(R^{13})_p$	$(R^{10})_p$
CF_3	1	CH_2COOH	-		$CH_2COOt\text{-}Bu$	-		H
OH	1	CH_2COOH	-		$CH_2COOt\text{-}Bu$	-		H
NO_2	1	CH_2COOH	-		$CH_2COOt\text{-}Bu$	-		H
H	1	CH_2CH_3	-		$CH_2COOt\text{-}Bu$	-		H
OH	1	CH_2CH_3	-		$CH_2COOt\text{-}Bu$	-		H
H	1	CH_2COOEt	-		$CH_2COOt\text{-}Bu$	-		H
OH	1	CH_2COOEt	-		$CH_2COOt\text{-}Bu$	-		H
H	1	CH_2CH_2COOH	-		$CH_2COOt\text{-}Bu$	-		H
OH	1	CH_2CH_2COOH	-		$CH_2COOt\text{-}Bu$	-		H
H	1	H	-		CH_2COOEt	-		H
Cl	1	H	-		CH_2COOEt	-		H
F	1	H	-		CH_2COOEt	-		H
CF_3	1	H	-		CH_2COOEt	-		H
OH	1	H	-		CH_2COOEt	-		H
NO_2	1	H	-		CH_2COOEt	-		H
H	1	CH_3	-		CH_2COOEt	-		H
Cl	1	CH_3	-		CH_2COOEt	-		H
F	1	CH_3	-		CH_2COOEt	-		H
CF_3	1	CH_3	-		CH_2COOEt	-		H
OH	1	CH_3	-		CH_2COOEt	-		H
NO_2	1	CH_3	-		CH_2COOEt	-		H
H	1	CH_2COOH	-		CH_2COOEt	-		H
Cl	1	CH_2COOH	-		CH_2COOEt	-		H
F	1	CH_2COOH	-		CH_2COOEt	-		H
CF_3	1	CH_2COOH	-		CH_2COOEt	-		H
OH	1	CH_2COOH	-		CH_2COOEt	-		H
NO_2	1	CH_2COOH	-		CH_2COOEt	-		H
H	1	CH_2CH_3	-		CH_2COOEt	-		H
OH	1	CH_2CH_3	-		CH_2COOEt	-		H
H	1	CH_2COOEt	-		CH_2COOEt	-		H

TABLE 5 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
OH	1	CH_2COOEt	-	CH_2COOEt	-	H
H	1	CH_2CH_2COOH	-	CH_2COOEt	-	H
OH	1	CH_2CH_2COOH	-	CH_2COOEt	-	H

TABLE 6



X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
H	1	H	-	Ph	-	H
Cl	1	H	-	Ph	-	H
F	1	H	-	Ph	-	H
CF_3	1	H	-	Ph	-	H
OH	1	H	-	Ph	-	H
NO_2	1	H	-	Ph	-	H
H	1	CH_3	-	Ph	-	H
Cl	1	CH_3	-	Ph	-	H
F	1	CH_3	-	Ph	-	H
CF_3	1	CH_3	-	Ph	-	H
OH	1	CH_3	-	Ph	-	H
NO_2	1	CH_3	-	Ph	-	H
H	1	CH_2COOH	-	Ph	-	H
Cl	1	CH_2COOH	-	Ph	-	H
F	1	CH_2COOH	-	Ph	-	H
CF_3	1	CH_2COOH	-	Ph	-	H
OH	1	CH_2COOH	-	Ph	-	H
NO_2	1	CH_2COOH	-	Ph	-	H
H	1	CH_2CH_3	-	Ph	-	H

TABLE 6 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
OH	1	CH_2CH_3	-	Ph	-	H
H	1	CH_2COOEt	-	Ph	-	H
OH	1	CH_2COOEt	-	Ph	-	H
H	1	CH_2CH_2COOH	-	Ph	-	H
OH	1	CH_2CH_2COOH	-	Ph	-	H
H	1	H	-	o-F-Ph	-	H
Cl	1	H	-	o-F-Ph	-	H
F	1	H	-	o-F-Ph	-	H
CF_3	1	H	-	o-F-Ph	-	H
OH	1	H	-	o-F-Ph	-	H
NO_2	1	H	-	o-F-Ph	-	H
H	1	CH_3	-	o-F-Ph	-	H
Cl	1	CH_3	-	o-F-Ph	-	H
F	1	CH_3	-	o-F-Ph	-	H
CF_3	1	CH_3	-	o-F-Ph	-	H
OH	1	CH_3	-	o-F-Ph	-	H
NO_2	1	CH_3	-	o-F-Ph	-	H
H	1	CH_2COOH	-	o-F-Ph	-	H
Cl	1	CH_2COOH	-	o-F-Ph	-	H
F	1	CH_2COOH	-	o-F-Ph	-	H
CF_3	1	CH_2COOH	-	o-F-Ph	-	H
OH	1	CH_2COOH	-	o-F-Ph	-	H
NO_2	1	CH_2COOH	-	o-F-Ph	-	H
H	1	CH_2CH_3	-	o-F-Ph	-	H
OH	1	CH_2CH_3	-	o-F-Ph	-	H
H	1	CH_2COOEt	-	o-F-Ph	-	H
OH	1	CH_2COOEt	-	o-F-Ph	-	H
H	1	CH_2CH_2COOH	-	o-F-Ph	-	H
OH	1	CH_2CH_2COOH	-	o-F-Ph	-	H

TABLE 6 (cont'd)

	X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
5	H	1	H	-	p-Cl-Ph	-	H
	F	1	H	-	p-Cl-Ph	-	H
	CF_3	1	H	-	p-Cl-Ph	-	H
	OH	1	H	-	p-Cl-Ph	-	H
	H	1	CH_3	-	p-Cl-Ph	-	H
10	F	1	CH_3	-	p-Cl-Ph	-	H
	CF_3	1	CH_3	-	p-Cl-Ph	-	H
	OH	1	CH_3	-	p-Cl-Ph	-	H
	H	1	CH_2COOH	-	p-Cl-Ph	-	H
	F	1	CH_2COOH	-	p-Cl-Ph	-	H
15	CF_3	1	CH_2COOH	-	p-Cl-Ph	-	H
	OH	1	CH_2COOH	-	p-Cl-Ph	-	H
	H	1	CH_2CH_3	-	p-Cl-Ph	-	H
	H	1	CH_2COOEt	-	p-Cl-Ph	-	H
	H	1	CH_2CH_2COOH	-	p-Cl-Ph	-	H
20	H	1	H	-	CH_2COOt-Bu	-	H
	Cl	1	H	-	CH_2COOt-Bu	-	H
	F	1	H	-	CH_2COOt-Bu	-	H
	CF_3	1	H	-	CH_2COOt-Bu	-	H
	OH	1	H	-	CH_2COOt-Bu	-	H
25	NO_2	1	H	-	CH_2COOt-Bu	-	H
	H	1	CH_3	-	CH_2COOt-Bu	-	H
	Cl	1	CH_3	-	CH_2COOt-Bu	-	H
	F	1	CH_3	-	CH_2COOt-Bu	-	H
	CF_3	1	CH_3	-	CH_2COOt-Bu	-	H
30	OH	1	CH_3	-	CH_2COOt-Bu	-	H
	NO_2	1	CH_3	-	CH_2COOt-Bu	-	H
	H	1	CH_2COOH	-	CH_2COOt-Bu	-	H
	Cl	1	CH_2COOH	-	CH_2COOt-Bu	-	H
	F	1	CH_2COOH	-	CH_2COOt-Bu	-	H

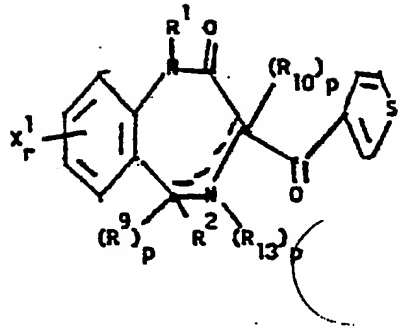
TABLE 6 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
CF_3	1	CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
OH	1	CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
NO_2	1	CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
H	1	CH_2CH_3	-	$CH_2COOt\text{-}Bu$	-	H
OH	1	CH_2CH_3	-	$CH_2COOt\text{-}Bu$	-	H
H	1	CH_2COOEt	-	$CH_2COOt\text{-}Bu$	-	H
OH	1	CH_2COOEt	-	$CH_2COOt\text{-}Bu$	-	H
H	1	CH_2CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
OH	1	CH_2CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
H	1	H	-	CH_2COOEt	-	H
Cl	1	H	-	CH_2COOEt	-	H
F	1	H	-	CH_2COOEt	-	H
CF_3	1	H	-	CH_2COOEt	-	H
OH	1	H	-	CH_2COOEt	-	H
NO_2	1	H	-	CH_2COOEt	-	H
H	1	CH_3	-	CH_2COOEt	-	H
Cl	1	CH_3	-	CH_2COOEt	-	H
F	1	CH_3	-	CH_2COOEt	-	H
CF_3	1	CH_3	-	CH_2COOEt	-	H
OH	1	CH_3	-	CH_2COOEt	-	H
NO_2	1	CH_3	-	CH_2COOEt	-	H
H	1	CH_2COOH	-	CH_2COOEt	-	H
Cl	1	CH_2COOH	-	CH_2COOEt	-	H
F	1	CH_2COOH	-	CH_2COOEt	-	H
CF_3	1	CH_2COOH	-	CH_2COOEt	-	H
OH	1	CH_2COOH	-	CH_2COOEt	-	H
NO_2	1	CH_2COOH	-	CH_2COOEt	-	H
H	1	CH_2CH_3	-	CH_2COOEt	-	H
OH	1	CH_2CH_3	-	CH_2COOEt	-	H
H	1	CH_2COOEt	-	CH_2COOEt	-	H

TABLE 6 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
OH	1	CH_2COOEt	-	CH_2COOEt	-	H
H	1	CH_2CH_2COOH	-	CH_2COOEt	-	H
OH	1	CH_2CH_2COOH	-	CH_2COOEt	-	H

TABLE 7



X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
H	1	H	-	Ph	-	H
Cl	1	H	-	Ph	-	H
F	1	H	-	Ph	-	H
CF_3	1	H	-	Ph	-	H
OH	1	H	-	Ph	-	H
NO_2	1	H	-	Ph	-	H
H	1	CH_3	-	Ph	-	H
Cl	1	CH_3	-	Ph	-	H
F	1	CH_3	-	Ph	-	H
CF_3	1	CH_3	-	Ph	-	H
OH	1	CH_3	-	Ph	-	H
NO_2	1	CH_3	-	Ph	-	H
H	1	CH_2COOH	-	Ph	-	H
Cl	1	CH_2COOH	-	Ph	-	H
F	1	CH_2COOH	-	Ph	-	H
CF_3	1	CH_2COOH	-	Ph	-	H
OH	1	CH_2COOH	-	Ph	-	H
NO_2	1	CH_2COOH	-	Ph	-	H
H	1	CH_2CH_3	-	Ph	-	H
OH	1	CH_2CH_3	-	Ph	-	H
H	1	CH_2COOEt	-	Ph	-	H

TABLE 7 (cont'd)

	X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
5	OH	1	CH_2COOEt	-	Ph	-	H
	H	1	CH_2CH_2COOH	-	Ph	-	H
	OH	1	CH_2CH_2COOH	-	Ph	-	H
	H	1	H	-	o-F-Ph	-	H
	Cl	1	H	-	o-F-Ph	-	H
10	F	1	H	-	o-F-Ph	-	H
	CF_3	1	H	-	o-F-Ph	-	H
	OH	1	H	-	o-F-Ph	-	H
	NO_2	1	H	-	o-F-Ph	-	H
	H	1	CH_3	-	o-F-Ph	-	H
15	Cl	1	CH_3	-	o-F-Ph	-	H
	F	1	CH_3	-	o-F-Ph	-	H
	CF_3	1	CH_3	-	o-F-Ph	-	H
	OH	1	CH_3	-	o-F-Ph	-	H
	NO_2	1	CH_3	-	o-F-Ph	-	H
20	H	1	CH_2COOH	-	o-F-Ph	-	H
	Cl	1	CH_2COOH	-	o-F-Ph	-	H
	F	1	CH_2COOH	-	o-F-Ph	-	H
	CF_3	1	CH_2COOH	-	o-F-Ph	-	H
	OH	1	CH_2COOH	-	o-F-Ph	-	H
25	NO_2	1	CH_2COOH	-	o-F-Ph	-	H
	H	1	CH_2CH_3	-	o-F-Ph	-	H
	OH	1	CH_2CH_3	-	o-F-Ph	-	H
	H	1	CH_2COOEt	-	o-F-Ph	-	H
	OH	1	CH_2COOEt	-	o-F-Ph	-	H
30	H	1	CH_2CH_2COOH	-	o-F-Ph	-	H
	OH	1	CH_2CH_2COOH	-	o-F-Ph	-	H
	H	1	H	-	p-Cl-Ph	-	H
	F	1	H	-	p-Cl-Ph	-	H

TABLE 1 (cont'd)

	X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
	CF_3	1	H	-	p-Cl-Ph	-	H
	OH	1	H	-	p-Cl-Ph	-	H
	H	1	CH_3	-	p-Cl-Ph	-	H
	F	1	CH_3	-	p-Cl-Ph	-	H
	CF_3	1	CH_3	-	p-Cl-Ph	-	H
	OH	1	CH_3	-	p-Cl-Ph	-	H
	H	1	CH_2COOH	-	p-Cl-Ph	-	H
	F	1	CH_2COOH	-	p-Cl-Ph	-	H
	CF_3	1	CH_2COOH	-	p-Cl-Ph	-	H
	OH	1	CH_2COOH	-	p-Cl-Ph	-	H
	H	1	CH_2CH_3	-	p-Cl-Ph	-	H
	H	1	CH_2COOEt	-	p-Cl-Ph	-	H
	H	1	CH_2CH_2COOH	-	p-Cl-Ph	-	H
	H	1	H	-	CH_2COOt-Bu	-	H
	Cl	1	H	-	CH_2COOt-Bu	-	H
	F	1	H	-	CH_2COOt-Bu	-	H
	CF_3	1	H	-	CH_2COOt-Bu	-	H
	OH	1	H	-	CH_2COOt-Bu	-	H
	NO_2	1	H	-	CH_2COOt-Bu	-	H
	H	1	CH_3	-	CH_2COOt-Bu	-	H
	Cl	1	CH_3	-	CH_2COOt-Bu	-	H
	F	1	CH_3	-	CH_2COOt-Bu	-	H
	CF_3	1	CH_3	-	CH_2COOt-Bu	-	H
	OH	1	CH_3	-	CH_2COOt-Bu	-	H
	NO_2	1	CH_3	-	CH_2COOt-Bu	-	H
	H	1	CH_2COOH	-	CH_2COOt-Bu	-	H
	Cl	1	CH_2COOH	-	CH_2COOt-Bu	-	H
	F	1	CH_2COOH	-	CH_2COOt-Bu	-	H
	CF_3	1	CH_2COOH	-	CH_2COOt-Bu	-	H
	OH	1	CH_2COOH	-	CH_2COOt-Bu	-	H

TABLE 7 (cont'd)

	X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
	NO_2	1	CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
	H	1	CH_2CH_3	-	$CH_2COOt\text{-}Bu$	-	H
	OH	1	CH_2CH_3	-	$CH_2COOt\text{-}Bu$	-	H
	H	1	CH_2COOEt	-	$CH_2COOt\text{-}Bu$	-	H
	OH	1	CH_2COOEt	-	$CH_2COOt\text{-}Bu$	-	H
	H	1	CH_2CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
	OH	1	CH_2CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
	H	1	H	-	CH_2COOEt	-	H
	Cl	1	H	-	CH_2COOEt	-	H
	F	1	H	-	CH_2COOEt	-	H
	CF_3	1	H	-	CH_2COOEt	-	H
	OH	1	H	-	CH_2COOEt	-	H
	NO_2	1	H	-	CH_2COOEt	-	H
	H	1	CH_3	-	CH_2COOEt	-	H
	Cl	1	CH_3	-	CH_2COOEt	-	H
	F	1	CH_3	-	CH_2COOEt	-	H
	CF_3	1	CH_3	-	CH_2COOEt	-	H
	OH	1	CH_3	-	CH_2COOEt	-	H
	NO_2	1	CH_3	-	CH_2COOEt	-	H
	H	1	CH_2COOH	-	CH_2COOEt	-	H
	Cl	1	CH_2COOH	-	CH_2COOEt	-	H
	F	1	CH_2COOH	-	CH_2COOEt	-	H
	CF_3	1	CH_2COOH	-	CH_2COOEt	-	H
	OH	1	CH_2COOH	-	CH_2COOEt	-	H
	NO_2	1	CH_2COOH	-	CH_2COOEt	-	H
	H	1	CH_2CH_3	-	CH_2COOEt	-	H
	OH	1	CH_2CH_3	-	CH_2COOEt	-	H
	H	1	CH_2COOEt	-	CH_2COOEt	-	H
	OH	1	CH_2COOEt	-	CH_2COOEt	-	H
	H	1	CH_2CH_2COOH	-	CH_2COOEt	-	H

TABLE 7 (cont'd)

X^1	p	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
OH	1	CH_2CH_2COOH	-	CH_2COOEt	-	H
H	1	CH_3	-	Ph	-	OH
H	1	CH_2CH_3	-	Ph	-	OH
H	1	CH_2COOEt	-	Ph	-	OH
H	1	CH_3	-	o-F-Ph	-	OH
H	1	CH_2CH_3	-	o-F-Ph	-	OH
H	1	CH_2COOEt	-	o-F-Ph	-	OH
H	1	CH_3	-	CH_2COOt-Bu	-	OH
H	1	CH_2CH_3	-	CH_2COOt-Bu	-	OH
H	1	CH_2COOEt	-	CH_2COOt-Bu	-	OH

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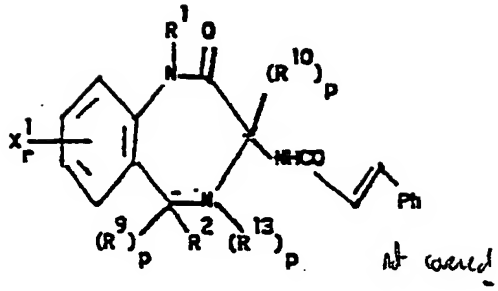
TABLE 8



X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
H	1	H	-	Ph	-	H
Cl	1	H	-	Ph	-	H
F	1	H	-	Ph	-	H
CF_3	1	H	-	Ph	-	H
OH	1	H	-	Ph	-	H
NO_2	1	H	-	Ph	-	H
H	1	CH_3	-	Ph	-	H
Cl	1	CH_3	-	Ph	-	H
F	1	CH_3	-	Ph	-	H
CF_3	1	CH_3	-	Ph	-	H
OH	1	CH_3	-	Ph	-	H
NO_2	1	CH_3	-	Ph	-	H
H	1	CH_2COOH	-	Ph	-	H
Cl	1	CH_2COOH	-	Ph	-	H
F	1	CH_2COOH	-	Ph	-	H
CF_3	1	CH_2COOH	-	Ph	-	H
OH	1	CH_2COOH	-	Ph	-	H
NO_2	1	CH_2COOH	-	Ph	-	H
H	1	CH_2CH_3	-	Ph	-	H
OH	1	CH_2CH_3	-	Ph	-	H
H	1	CH_2COOEt	-	Ph	-	H

TABLE 8 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
OH	1	CH_2COOEt	-	Ph	-	H
H	1	CH_2CH_2COOH	-	Ph	-	H
OH	1	CH_2CH_2COOH	-	Ph	-	H
H	1	H	-	o-F-Ph	-	H
Cl	1	H	-	o-F-Ph	-	H
F	1	H	-	o-F-Ph	-	H
CF_3	1	H	-	o-F-Ph	-	H
OH	1	H	-	o-F-Ph	-	H
NO_2	1	H	-	o-F-Ph	-	H
H	1	CH_3	-	o-F-Ph	-	H
Cl	1	CH_3	-	o-F-Ph	-	H
F	1	CH_3	-	o-F-Ph	-	H
CF_3	1	CH_3	-	o-F-Ph	-	H
OH	1	CH_3	-	o-F-Ph	-	H
NO_2	1	CH_3	-	o-F-Ph	-	H
H	1	CH_2COOH	-	o-F-Ph	-	H
Cl	1	CH_2COOH	-	o-F-Ph	-	H
F	1	CH_2COOH	-	o-F-Ph	-	H
CF_3	1	CH_2COOH	-	o-F-Ph	-	H
OH	1	CH_2COOH	-	o-F-Ph	-	H
NO_2	1	CH_2COOH	-	o-F-Ph	-	H
H	1	CH_2CH_3	-	o-F-Ph	-	H
OH	1	CH_2CH_3	-	o-F-Ph	-	H
H	1	CH_2COOEt	-	o-F-Ph	-	H
OH	1	CH_2COOEt	-	o-F-Ph	-	H
H	1	CH_2CH_2COOH	-	o-F-Ph	-	H
OH	1	CH_2CH_2COOH	-	o-F-Ph	-	H
H	1	H	-	p-Cl-Ph	-	H
F	1	H	-	p-Cl-Ph	-	H
CF_3	1	H	-	p-Cl-Ph	-	H

TABLE 8 (cont'd)

	X^1	r	R^1		$(R^9)_p$	R^2		$(R^{13})_p$	$(R^{10})_p$
5	OH	1	H	-		p-Cl-Ph	-		H
	H	1	CH_3	-		p-Cl-Ph	-		H
	F	1	CH_3	-		p-Cl-Ph	-		H
	CF_3	1	CH_3	-		p-Cl-Ph	-		H
	OH	1	CH_3	-		p-Cl-Ph	-		H
10	H	1	CH_2COOH	-		p-Cl-Ph	-		H
	F	1	CH_2COOH	-		p-Cl-Ph	-		H
	CF_3	1	CH_2COOH	-		p-Cl-Ph	-		H
	OH	1	CH_2COOH	-		p-Cl-Ph	-		H
	H	1	CH_2CH_3	-		p-Cl-Ph	-		H
15	H	1	CH_2COOEt	-		p-Cl-Ph	-		H
	H	1	CH_2CH_2COOH	-		p-Cl-Ph	-		H
	H	1	H	-		CH_2COOt-Bu	-		H
	Cl	1	H	-		CH_2COOt-Bu	-		H
	F	1	H	-		CH_2COOt-Bu	-		H
20	CF_3	1	H	-		CH_2COOt-Bu	-		H
	OH	1	H	-		CH_2COOt-Bu	-		H
	NO_2	1	H	-		CH_2COOt-Bu	-		H
	H	1	CH_3	-		CH_2COOt-Bu	-		H
	Cl	1	CH_3	-		CH_2COOt-Bu	-		H
25	F	1	CH_3	-		CH_2COOt-Bu	-		H
	CF_3	1	CH_3	-		CH_2COOt-Bu	-		H
	OH	1	CH_3	-		CH_2COOt-Bu	-		H
	NO_2	1	CH_3	-		CH_2COOt-Bu	-		H
	H	1	CH_2COOH	-		CH_2COOt-Bu	-		H
30	Cl	1	CH_2COOH	-		CH_2COOt-Bu	-		H
	F	1	CH_2COOH	-		CH_2COOt-Bu	-		H
	CF_3	1	CH_2COOH	-		CH_2COOt-Bu	-		H
	OH	1	CH_2COOH	-		CH_2COOt-Bu	-		H
	NO_2	1	CH_2COOH	-		CH_2COOt-Bu	-		H

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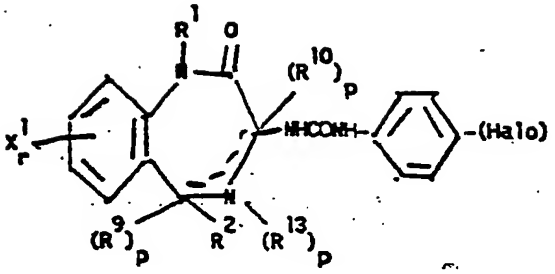
TABLE 8 (cont'd)

	X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
	H	1	CH_2CH_3	-	$CH_2COOt\text{-}Bu$	-	H
	OH	1	CH_2CH_3	-	$CH_2COOt\text{-}Bu$	-	H
	H	1	CH_2COOEt	-	$CH_2COOt\text{-}Bu$	-	H
	OH	1	CH_2COOEt	-	$CH_2COOt\text{-}Bu$	-	H
	H	1	CH_2CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
	OH	1	CH_2CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
	H	1	H	-	CH_2COOEt	-	H
	Cl	1	H	-	CH_2COOEt	-	H
	F	1	H	-	CH_2COOEt	-	H
	CF_3	1	H	-	CH_2COOEt	-	H
	OH	1	H	-	CH_2COOEt	-	H
	NO_2	1	H	-	CH_2COOEt	-	H
	H	1	CH_3	-	CH_2COOEt	-	H
	Cl	1	CH_3	-	CH_2COOEt	-	H
	F	1	CH_3	-	CH_2COOEt	-	H
	CF_3	1	CH_3	-	CH_2COOEt	-	H
	OH	1	CH_3	-	CH_2COOEt	-	H
	NO_2	1	CH_3	-	CH_2COOEt	-	H
	H	1	CH_2COOH	-	CH_2COOEt	-	H
	Cl	1	CH_2COOH	-	CH_2COOEt	-	H
	F	1	CH_2COOH	-	CH_2COOEt	-	H
	CF_3	1	CH_2COOH	-	CH_2COOEt	-	H
	OH	1	CH_2COOH	-	CH_2COOEt	-	H
	NO_2	1	CH_2COOH	-	CH_2COOEt	-	H
	H	1	CH_2CH_3	-	CH_2COOEt	-	H
	OH	1	CH_2CH_3	-	CH_2COOEt	-	H
	H	1	CH_2COOEt	-	CH_2COOEt	-	H
	OH	1	CH_2COOEt	-	CH_2COOEt	-	H
	H	1	CH_2CH_2COOH	-	CH_2COOEt	-	H
	OH	1	CH_2CH_2COOH	-	CH_2COOEt	-	H

TABLE 9



X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
H	1	H	-	Ph	-	H
Cl	1	H	-	Ph	-	H
F	1	H	-	Ph	-	H
CF_3	1	H	-	Ph	-	H
OH	1	H	-	Ph	-	H
NO_2	1	H	-	Ph	-	H
H	1	CH_3	-	Ph	-	H
Cl	1	CH_3	-	Ph	-	H
F	1	CH_3	-	Ph	-	H
CF_3	1	CH_3	-	Ph	-	H
OH	1	CH_3	-	Ph	-	H
NO_2	1	CH_3	-	Ph	-	H
H	1	CH_2COOH	-	Ph	-	H
Cl	1	CH_2COOH	-	Ph	-	H
F	1	CH_2COOH	-	Ph	-	H
CF	1	CH_2COOH	-	Ph	-	H
OH	1	CH_2COOH	-	Ph	-	H
NO_2	1	CH_2COOH	-	Ph	-	H
H	1	CH_2CH_3	-	Ph	-	H
OH	1	CH_2CH_3	-	Ph	-	H
H	1	CH_2COOEt	-	Ph	-	H

TABLE 9 (cont'd)

	X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
5	OH	1	CH_2COOEt	-	Ph	-	H
	H	1	CH_2CH_2COOH	-	Ph	-	H
	OH	1	CH_2CH_2COOH	-	Ph	-	H
	H	1	H	-	o-F-Ph	-	H
	Cl	1	H	-	o-F-Ph	-	H
10	F	1	H	-	o-F-Ph	-	H
	CF_3	1	H	-	o-F-Ph	-	H
	OH	1	H	-	o-F-Ph	-	H
	NO_2	1	H	-	o-F-Ph	-	H
	H	1	CH_3	-	o-F-Ph	-	H
15	Cl	1	CH_3	-	o-F-Ph	-	H
	F	1	CH_3	-	o-F-Ph	-	H
	CF_3	1	CH_3	-	o-F-Ph	-	H
	OH	1	CH_3	-	o-F-Ph	-	H
	NO_2	1	CH_3	-	o-F-Ph	-	H
20	H	1	CH_2COOH	-	o-F-Ph	-	H
	Cl	1	CH_2COOH	-	o-F-Ph	-	H
	F	1	CH_2COOH	-	o-F-Ph	-	H
	CF_3	1	CH_2COOH	-	o-F-Ph	-	H
	OH	1	CH_2COOH	-	o-F-Ph	-	H
25	NO_2	1	CH_2COOH	-	o-F-Ph	-	H
	H	1	CH_2CH_3	-	o-F-Ph	-	H
	OH	1	CH_2CH_3	-	o-F-Ph	-	H
	H	1	CH_2COOEt	-	o-F-Ph	-	H
	OH	1	CH_2COOEt	-	o-F-Ph	-	H
30	H	1	CH_2CH_2COOH	-	o-F-Ph	-	H
	OH	1	CH_2CH_2COOH	-	o-F-Ph	-	H
	H	1	H	-	p-Cl-Ph	-	H
	F	1	H	-	p-Cl-Ph	-	H
	CF_3	1	H	-	p-Cl-Ph	-	H

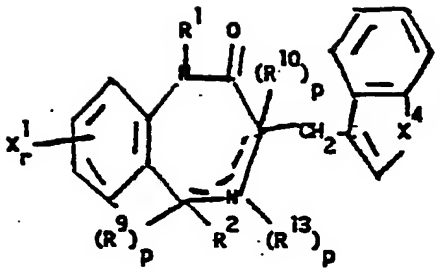
TABLE 9 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
OH	1	H	-	p-Cl-Ph	-	H
H	1	CH_3	-	p-Cl-Ph	-	H
F	1	CH_3	-	p-Cl-Ph	-	H
CF_3	1	CH_3	-	p-Cl-Ph	-	H
OH	1	CH_3	-	p-Cl-Ph	-	H
H	1	CH_2COOH	-	p-Cl-Ph	-	H
F	1	CH_2COOH	-	p-Cl-Ph	-	H
CF_3	1	CH_2COOH	-	p-Cl-Ph	-	H
OH	1	CH_2COOH	-	p-Cl-Ph	-	H
H	1	CH_2CH_3	-	p-Cl-Ph	-	H
H	1	CH_2COOEt	-	p-Cl-Ph	-	H
H	1	CH_2CH_2COOH	-	p-Cl-Ph	-	H
H	1	H	-	CH_2COOt-Bu	-	H
Cl	1	H	-	CH_2COOt-Bu	-	H
F	1	H	-	CH_2COOt-Bu	-	H
CF_3	1	H	-	CH_2COOt-Bu	-	H
OH	1	H	-	CH_2COOt-Bu	-	H
NO_2	1	H	-	CH_2COOt-Bu	-	H
H	1	CH_3	-	CH_2COOt-Bu	-	H
Cl	1	CH_3	-	CH_2COOt-Bu	-	H
F	1	CH_3	-	CH_2COOt-Bu	-	H
CF_3	1	CH_3	-	CH_2COOt-Bu	-	H
OH	1	CH_3	-	CH_2COOt-Bu	-	H
NO_2	1	CH_3	-	CH_2COOt-Bu	-	H
H	1	CH_2COOH	-	CH_2COOt-Bu	-	H
Cl	1	CH_2COOH	-	CH_2COOt-Bu	-	H
F	1	CH_2COOH	-	CH_2COOt-Bu	-	H
CF_3	1	CH_2COOH	-	CH_2COOt-Bu	-	H
OH	1	CH_2COOH	-	CH_2COOt-Bu	-	H
NO_2	1	CH_2COOH	-	CH_2COOt-Bu	-	H

TABLE 9 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
H	1	CH_2CH_3	-	$CH_2COOt\text{-}Bu$	-	H
OH	1	CH_2CH_3	-	$CH_2COOt\text{-}Bu$	-	H
H	1	CH_2COOEt	-	$CH_2COOt\text{-}Bu$	-	H
OH	1	CH_2COOEt	-	$CH_2COOt\text{-}Bu$	-	H
H	1	CH_2CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
OH	1	CH_2CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
H	1	H	-	CH_2COOEt	-	H
Cl	1	H	-	CH_2COOEt	-	H
F	1	H	-	CH_2COOEt	-	H
CF_3	1	H	-	CH_2COOEt	-	H
OH	1	H	-	CH_2COOEt	-	H
NO_2	1	H	-	CH_2COOEt	-	H
H	1	CH_3	-	CH_2COOEt	-	H
Cl	1	CH_3	-	CH_2COOEt	-	H
F	1	CH_3	-	CH_2COOEt	-	H
CF_3	1	CH_3	-	CH_2COOEt	-	H
OH	1	CH_3	-	CH_2COOEt	-	H
NO_2	1	CH_3	-	CH_2COOEt	-	H
H	1	CH_2COOH	-	CH_2COOEt	-	H
Cl	1	CH_2COOH	-	CH_2COOEt	-	H
F	1	CH_2COOH	-	CH_2COOEt	-	H
CF_3	1	CH_2COOH	-	CH_2COOEt	-	H
OH	1	CH_2COOH	-	CH_2COOEt	-	H
NO_2	1	CH_2COOH	-	CH_2COOEt	-	H
H	1	CH_2CH_3	-	CH_2COOEt	-	H
OH	1	CH_2CH_3	-	CH_2COOEt	-	H
H	1	CH_2COOEt	-	CH_2COOEt	-	H
OH	1	CH_2COOEt	-	CH_2COOEt	-	H
H	1	CH_2CH_2COOH	-	CH_2COOEt	-	H
OH	1	CH_2CH_2COOH	-	CH_2COOEt	-	H

TABLE 10



X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
H	1	H	-	Ph	-	H
Cl	1	H	-	Ph	-	H
F	1	H	-	Ph	-	H
CF_3	1	H	-	Ph	-	H
OH	1	H	-	Ph	-	H
NO_2	1	H	-	Ph	-	H
H	1	CH_3	-	Ph	-	H
Cl	1	CH_3	-	Ph	-	H
F	1	CH_3	-	Ph	-	H
CF_3	1	CH_3	-	Ph	-	H
OH	1	CH_3	-	Ph	-	H
NO_2	1	CH_3	-	Ph	-	H
H	1	CH_2COOH	-	Ph	-	H
Cl	1	CH_2COOH	-	Ph	-	H
F	1	CH_2COOH	-	Ph	-	H
CF_3	1	CH_2COOH	-	Ph	-	H
OH	1	CH_2COOH	-	Ph	-	H
NO_2	1	CH_2COOH	-	Ph	-	H
H	1	CH_2CH_3	-	Ph	-	H
OH	1	CH_2CH_3	-	Ph	-	H

TABLE 10 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
H	1	CH_2COOEt	-	Ph	-	H
OH	1	CH_2COOEt	-	Ph	-	H
H	1	CH_2CH_2COOH	-	Ph	-	H
OH	1	CH_2CH_2COOH	-	Ph	-	H
H	1	H	-	o-F-Ph	-	H
Cl	1	H	-	o-F-Ph	-	H
F	1	H	-	o-F-Ph	-	H
CF_3	1	H	-	o-F-Ph	-	H
OH	1	H	-	o-F-Ph	-	H
NO_2	1	H	-	o-F-Ph	-	H
H	1	CH_3	-	o-F-Ph	-	H
Cl	1	CH_3	-	o-F-Ph	-	H
F	1	CH_3	-	o-F-Ph	-	H
CF_3	1	CH_3	-	o-F-Ph	-	H
OH	1	CH_3	-	o-F-Ph	-	H
NO_2	1	CH_3	-	o-F-Ph	-	H
H	1	CH_2COOH	-	o-F-Ph	-	H
Cl	1	CH_2COOH	-	o-F-Ph	-	H
F	1	CH_2COOH	-	o-F-Ph	-	H
CF_3	1	CH_2COOH	-	o-F-Ph	-	H
OH	1	CH_2COOH	-	o-F-Ph	-	H
NO_2	1	CH_2COOH	-	o-F-Ph	-	H
H	1	CH_2CH_3	-	o-F-Ph	-	H
OH	1	CH_2CH_3	-	o-F-Ph	-	H
H	1	CH_2COOEt	-	o-F-Ph	-	H
OH	1	CH_2COOEt	-	o-F-Ph	-	H
H	1	CH_2CH_2COOH	-	o-F-Ph	-	H
OH	1	CH_2CH_2COOH	-	o-F-Ph	-	H
H	1	H	-	p-Cl-Ph	-	H

TABLE 10 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
F	1	H	-	p-Cl-Ph	-	H
CF_3	1	H	-	p-Cl-Ph	-	H
OH	1	H	-	p-Cl-Ph	-	H
H	1	CH_3	-	p-Cl-Ph	-	H
F	1	CH_3	-	p-Cl-Ph	-	H
CF_3	1	CH_3	-	p-Cl-Ph	-	H
OH	1	CH_3	-	p-Cl-Ph	-	H
H	1	CH_2COOH	-	p-Cl-Ph	-	H
F	1	CH_2COOH	-	p-Cl-Ph	-	H
CF_3	1	CH_2COOH	-	p-Cl-Ph	-	H
OH	1	CH_2COOH	-	p-Cl-Ph	-	H
H	1	CH_2CH_3	-	p-Cl-Ph	-	H
H	1	CH_2COOEt	-	p-Cl-Ph	-	H
H	1	CH_2CH_2COOH	-	p-Cl-Ph	-	H
H	1	H	-	CH_2COOt-Bu	-	H
Cl	1	H	-	CH_2COOt-Bu	-	H
F	1	H	-	CH_2COOt-Bu	-	H
CF_3	1	H	-	CH_2COOt-Bu	-	H
OH	1	H	-	CH_2COOt-Bu	-	H
NO_2	1	H	-	CH_2COOt-Bu	-	H
H	1	CH_3	-	CH_2COOt-Bu	-	H
Cl	1	CH_3	-	CH_2COOt-Bu	-	H
F	1	CH_3	-	CH_2COOt-Bu	-	H
CF_3	1	CH_3	-	CH_2COOt-Bu	-	H
OH	1	CH_3	-	CH_2COOt-Bu	-	H
NO_2	1	CH_3	-	CH_2COOt-Bu	-	H
H	1	CH_2COOH	-	CH_2COOt-Bu	-	H
Cl	1	CH_2COOH	-	CH_2COOt-Bu	-	H
F	1	CH_2COOH	-	CH_2COOt-Bu	-	H
CF_3	1	CH_2COOH	-	CH_2COOt-Bu	-	H

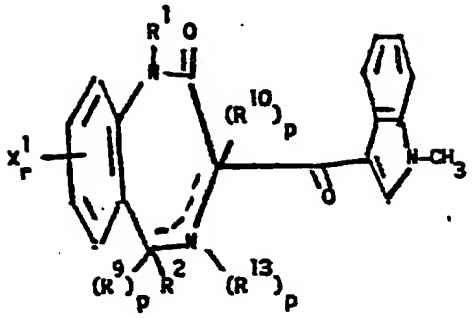
TABLE 10 (cont'd)

	X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
5	OH	1	CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
	NO_2	1	CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
	H	1	CH_2CH_3	-	$CH_2COOt\text{-}Bu$	-	H
	OH	1	CH_2CH_3	-	$CH_2COOt\text{-}Bu$	-	H
	H	1	CH_2COOEt	-	$CH_2COOt\text{-}Bu$	-	H
10	OH	1	CH_2COOEt	-	$CH_2COOt\text{-}Bu$	-	H
	H	1	CH_2CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
	OH	1	CH_2CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
	H	1	H	-	CH_2COOEt	-	H
	Cl	1	H	-	CH_2COOEt	-	H
15	F	1	H	-	CH_2COOEt	-	H
	CF_3	1	H	-	CH_2COOEt	-	H
	OH	1	H	-	CH_2COOEt	-	H
	NO_2	1	H	-	CH_2COOEt	-	H
	H	1	CH_3	-	CH_2COOEt	-	H
20	Cl	1	CH_3	-	CH_2COOEt	-	H
	F	1	CH_3	-	CH_2COOEt	-	H
	CF_3	1	CH_3	-	CH_2COOEt	-	H
	OH	1	CH_3	-	CH_2COOEt	-	H
	NO_2	1	CH_3	-	CH_2COOEt	-	H
25	H	1	CH_2COOH	-	CH_2COOEt	-	H
	Cl	1	CH_2COOH	-	CH_2COOEt	-	H
	F	1	CH_2COOH	-	CH_2COOEt	-	H
	CF_3	1	CH_2COOH	-	CH_2COOEt	-	H
	OH	1	CH_2COOH	-	CH_2COOEt	-	H
30	NO_2	1	CH_2COOH	-	CH_2COOEt	-	H
	H	1	CH_2CH_3	-	CH_2COOEt	-	H
	OH	1	CH_2CH_3	-	CH_2COOEt	-	H
	H	1	CH_2COOEt	-	CH_2COOEt	-	H

TABLE 10 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
OH	1	CH_2COOEt	-	CH_2COOEt	-	H
H	1	CH_2CH_2COOH	-	CH_2COOEt	-	H
OH	1	CH_2CH_2COOH	-	CH_2COOEt	-	H
H	1	CH_3	-	Ph	-	OH
H	1	CH_2CH_3	-	Ph	-	OH
H	1	CH_2COOEt	-	Ph	-	OH
H	1	CH_3	-	o-F-Ph	-	OH
H	1	CH_2CH_3	-	o-F-Ph	-	OH
H	1	CH_2COOEt	-	o-F-Ph	-	OH
H	1	CH_3	-	CH_2COOt-Bu	-	OH
H	1	CH_2CH_3	-	CH_2COOt-Bu	-	OH
H	1	CH_2COOEt	-	CH_2COOt-Bu	-	OH

TABLE 11



X^1_r	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
H	1	H	-	Ph	-	H
Cl	1	H	-	Ph	-	H
F	1	H	-	Ph	-	H
CF_3	1	H	-	Ph	-	H
OH	1	H	-	Ph	-	H
NO_2	1	H	-	Ph	-	H
H	1	CH_3	-	Ph	-	H
Cl	1	CH_3	-	Ph	-	H
F	1	CH_3	-	Ph	-	H
CF_3	1	CH_3	-	Ph	-	H
OH	1	CH_3	-	Ph	-	H
NO_2	1	CH_3	-	Ph	-	H
H	1	CH_2COOH	-	Ph	-	H
Cl	1	CH_2COOH	-	Ph	-	H
F	1	CH_2COOH	-	Ph	-	H
CF_3	1	CH_2COOH	-	Ph	-	H
OH	1	CH_2COOH	-	Ph	-	H
NO_2	1	CH_2COOH	-	Ph	-	H
H	1	CH_2CH_3	-	Ph	-	H
OH	1	CH_2CH_3	-	Ph	-	H
H	1	CH_2COOEt	-	Ph	-	H

TABLE 11 (cont'd)

	X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
5	OH	1	CH_2COOEt	-	Ph	-	H
	H	1	CH_2CH_2COOH	-	Ph	-	H
	OH	1	CH_2CH_2COOH	-	Ph	-	H
	H	1	H	-	o-F-Ph	-	H
	Cl	1	H	-	o-F-Ph	-	H
10	F	1	H	-	o-F-Ph	-	H
	CF_3	1	H	-	o-F-Ph	-	H
	OH	1	H	-	o-F-Ph	-	H
	NO_2	1	H	-	o-F-Ph	-	H
	H	1	CH_3	-	o-F-Ph	-	H
15	Cl	1	CH_3	-	o-F-Ph	-	H
	F	1	CH_3	-	o-F-Ph	-	H
	CF_3	1	CH_3	-	o-F-Ph	-	H
	OH	1	CH_3	-	o-F-Ph	-	H
	NO_2	1	CH_3	-	o-F-Ph	-	H
20	H	1	CH_2COOH	-	o-F-Ph	-	H
	Cl	1	CH_2COOH	-	o-F-Ph	-	H
	F	1	CH_2COOH	-	o-F-Ph	-	H
	CF_3	1	CH_2COOH	-	o-F-Ph	-	H
	OH	1	CH_2COOH	-	o-F-Ph	-	H
25	NO_2	1	CH_2COOH	-	o-F-Ph	-	H
	H	1	CH_2CH_3	-	o-F-Ph	-	H
	OH	1	CH_2CH_3	-	o-F-Ph	-	H
	H	1	CH_2COOEt	-	o-F-Ph	-	H
	OH	1	CH_2COOEt	-	o-F-Ph	-	H
30	H	1	CH_2CH_2COOH	-	o-F-Ph	-	H
	OH	1	CH_2CH_2COOH	-	o-F-Ph	-	H
	H	1	H	-	p-Cl-Ph	-	H
	F	1	H	-	p-Cl-Ph	-	H

TABLE 11 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
CF_3	1	H	-	p-Cl-Ph	-	H
OH	1	H	-	p-Cl-Ph	-	H
H	1	CH_3	-	p-Cl-Ph	-	H
F	1	CH_3	-	p-Cl-Ph	-	H
CF_3	1	CH_3	-	p-Cl-Ph	-	H
OH	1	CH_3	-	p-Cl-Ph	-	H
H	1	CH_2COOH	-	p-Cl-Ph	-	H
F	1	CH_2COOH	-	p-Cl-Ph	-	H
CF_3	1	CH_2COOH	-	p-Cl-Ph	-	H
OH	1	CH_2COOH	-	p-Cl-Ph	-	H
H	1	CH_2CH_3	-	p-Cl-Ph	-	H
H	1	CH_2COOEt	-	p-Cl-Ph	-	H
H	1	CH_2CH_2COOH	-	p-Cl-Ph	-	H
H	1	H	-	CH_2COOt-Bu	-	H
Cl	1	H	-	CH_2COOt-Bu	-	H
F	1	H	-	CH_2COOt-Bu	-	H
CF_3	1	H	-	CH_2COOt-Bu	-	H
OH	1	H	-	CH_2COOt-Bu	-	H
NO_2	1	H	-	CH_2COOt-Bu	-	H
H	1	CH_3	-	CH_2COOt-Bu	-	H
Cl	1	CH_3	-	CH_2COOt-Bu	-	H
F	1	CH_3	-	CH_2COOt-Bu	-	H
CF_3	1	CH_3	-	CH_2COOt-Bu	-	H
OH	1	CH_3	-	CH_2COOt-Bu	-	H
NO_2	1	CH_3	-	CH_2COOt-Bu	-	H
H	1	CH_2COOH	-	CH_2COOt-Bu	-	H
Cl	1	CH_2COOH	-	CH_2COOt-Bu	-	H
F	1	CH_2COOH	-	CH_2COOt-Bu	-	H
CF_3	1	CH_2COOH	-	CH_2COOt-Bu	-	H
OH	1	CH_2COOH	-	CH_2COOt-Bu	-	H

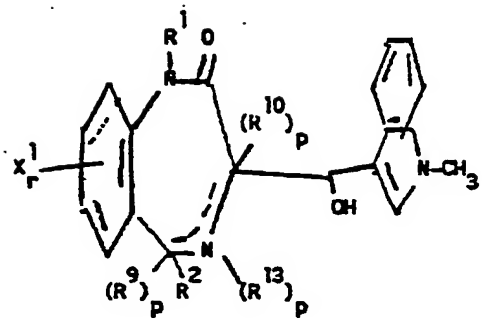
TABLE 11 (cont'd)

	X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
5	NO_2	1	CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
	H	1	CH_2CH_3	-	$CH_2COOt\text{-}Bu$	-	H
	OH	1	CH_2CH_3	-	$CH_2COOt\text{-}Bu$	-	H
	H	1	CH_2COOEt	-	$CH_2COOt\text{-}Bu$	-	H
	OH	1	CH_2COOEt	-	$CH_2COOt\text{-}Bu$	-	H
10	H	1	CH_2CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
	OH	1	CH_2CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
	H	1	H	-	CH_2COOEt	-	H
	Cl	1	H	-	CH_2COOEt	-	H
	F	1	H	-	CH_2COOEt	-	H
15	CF_3	1	H	-	CH_2COOEt	-	H
	OH	1	H	-	CH_2COOEt	-	H
	NO_2	1	H	-	CH_2COOEt	-	H
	H	1	CH_3	-	CH_2COOEt	-	H
	Cl	1	CH_3	-	CH_2COOEt	-	H
20	F	1	CH_3	-	CH_2COOEt	-	H
	CF_3	1	CH_3	-	CH_2COOEt	-	H
	OH	1	CH_3	-	CH_2COOEt	-	H
	NO_2	1	CH_3	-	CH_2COOEt	-	H
	H	1	CH_2COOH	-	CH_2COOEt	-	H
25	Cl	1	CH_2COOH	-	CH_2COOEt	-	H
	F	1	CH_2COOH	-	CH_2COOEt	-	H
	CF_3	1	CH_2COOH	-	CH_2COOEt	-	H
	OH	1	CH_2COOH	-	CH_2COOEt	-	H
	NO_2	1	CH_2COOH	-	CH_2COOEt	-	H
30	H	1	CH_2CH_3	-	CH_2COOEt	-	H
	OH	1	CH_2CH_3	-	CH_2COOEt	-	H
	H	1	CH_2COOEt	-	CH_2COOEt	-	H
	OH	1	CH_2COOEt	-	CH_2COOEt	-	H
	H	1	CH_2CH_2COOH	-	CH_2COOEt	-	H

TABLE 11 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
OH	1	CH_2CH_2COOH	-	CH_2COOEt	-	H
H	1	CH_3	-	Ph	-	OH
H	1	CH_2CH_3	-	Ph	-	OH
H	1	CH_2COOEt	-	Ph	-	OH
H	1	CH_3	-	o-F-Ph	-	OH
H	1	CH_2CH_3	-	o-F-Ph	-	OH
H	1	CH_2COOEt	-	o-F-Ph	-	OH
H	1	CH_3	-	CH_2COOt-Bu	-	OH
H	1	CH_2CH_3	-	CH_2COOt-Bu	-	OH
H	1	CH_2COOEt	-	CH_2COOt-Bu	-	OH

TABLE 12



X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
H	1	H	-	Ph	-	H
Cl	1	H	-	Ph	-	H
F	1	H	-	Ph	-	H
CF_3	1	H	-	Ph	-	H
OH	1	H	-	Ph	-	H
NO_2	1	H	-	Ph	-	H
H	1	CH_3	-	Ph	-	H
Cl	1	CH_3	-	Ph	-	H
F	1	CH_3	-	Ph	-	H
CF_3	1	CH_3	-	Ph	-	H
OH	1	CH_3	-	Ph	-	H
NO_2	1	CH_3	-	Ph	-	H
H	1	CH_2COOH	-	Ph	-	H
Cl	1	CH_2COOH	-	Ph	-	H
F	1	CH_2COOH	-	Ph	-	H
CF_3	1	CH_2COOH	-	Ph	-	H
OH	1	CH_2COOH	-	Ph	-	H
NO_2	1	CH_2COOH	-	Ph	-	H
H	1	CH_2CH_3	-	Ph	-	H
OH	1	CH_2CH_3	-	Ph	-	H

TABLE 12 (cont'd)

X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
H	1	CH_2COOEt	-	Ph	-	H
OH	1	CH_2COOEt	-	Ph	-	H
H	1	CH_2CH_2COOH	-	Ph	-	H
OH	1	CH_2CH_2COOH	-	Ph	-	H
H	1	H	-	o-F-Ph	-	H
Cl	1	H	-	o-F-Ph	-	H
F	1	H	-	o-F-Ph	-	H
CF_3	1	H	-	o-F-Ph	-	H
OH	1	H	-	o-F-Ph	-	H
NO_2	1	H	-	o-F-Ph	-	H
H	1	CH_3	-	o-F-Ph	-	H
Cl	1	CH_3	-	o-F-Ph	-	H
F	1	CH_3	-	o-F-Ph	-	H
CF_3	1	CH_3	-	o-F-Ph	-	H
OH	1	CH_3	-	o-F-Ph	-	H
NO_2	1	CH_3	-	o-F-Ph	-	H
H	1	CH_2COOH	-	o-F-Ph	-	H
Cl	1	CH_2COOH	-	o-F-Ph	-	H
F	1	CH_2COOH	-	o-F-Ph	-	H
CF_3	1	CH_2COOH	-	o-F-Ph	-	H
OH	1	CH_2COOH	-	o-F-Ph	-	H
NO_2	1	CH_2COOH	-	o-F-Ph	-	H
H	1	CH_2CH_3	-	o-F-Ph	-	H
OH	1	CH_2CH_3	-	o-F-Ph	-	H
H	1	CH_2COOEt	-	o-F-Ph	-	H
OH	1	CH_2COOEt	-	o-F-Ph	-	H
H	1	CH_2CH_2COOH	-	o-F-Ph	-	H
OH	1	CH_2CH_2COOH	-	o-F-Ph	-	H
H	1	H	-	p-Cl-Ph	-	H
F	1	H	-	p-Cl-Ph	-	H

TABLE 12 (cont'd)

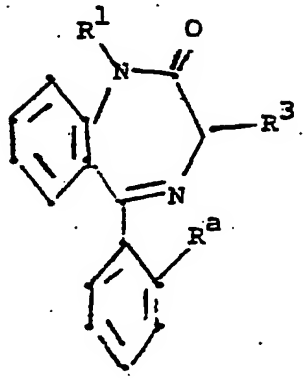
	X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
5	CF_3	1	H	-	p-Cl-Ph	-	H
	OH	1	H	-	p-Cl-Ph	-	H
	H	1	CH_3	-	p-Cl-Ph	-	H
	F	1	CH_3	-	p-Cl-Ph	-	H
	CF_3	1	CH_3	-	p-Cl-Ph	-	H
10	OH	1	CH_3	-	p-Cl-Ph	-	H
	H	1	CH_2COOH	-	p-Cl-Ph	-	H
	F	1	CH_2COOH	-	p-Cl-Ph	-	H
	CF_3	1	CH_2COOH	-	p-Cl-Ph	-	H
	OH	1	CH_2COOH	-	p-Cl-Ph	-	H
15	H	1	CH_2CH_3	-	p-Cl-Ph	-	H
	H	1	CH_2COOEt	-	p-Cl-Ph	-	H
	H	1	CH_2CH_2COOH	-	p-Cl-Ph	-	H
	H	1	H	-	CH_2COOt-Bu	-	H
	Cl	1	H	-	CH_2COOt-Bu	-	H
20	F	1	H	-	CH_2COOt-Bu	-	H
	CF_3	1	H	-	CH_2COOt-Bu	-	H
	OH	1	H	-	CH_2COOt-Bu	-	H
	NO_2	1	H	-	CH_2COOt-Bu	-	H
	H	1	CH_3	-	CH_2COOt-Bu	-	H
25	Cl	1	CH_3	-	CH_2COOt-Bu	-	H
	F	1	CH_3	-	CH_2COOt-Bu	-	H
	CF_3	1	CH_3	-	CH_2COOt-Bu	-	H
	OH	1	CH_3	-	CH_2COOt-Bu	-	H
	NO_2	1	CH_3	-	CH_2COOt-Bu	-	H
30	H	1	CH_2COOH	-	CH_2COOt-Bu	-	H
	Cl	1	CH_2COOH	-	CH_2COOt-Bu	-	H
	F	1	CH_2COOH	-	CH_2COOt-Bu	-	H
	CF_3	1	CH_2COOH	-	CH_2COOt-Bu	-	H
	OH	1	CH_2COOH	-	CH_2COOt-Bu	-	H

TABLE 12 (cont'd)

	X^1	r	R^1	$(R^9)_p$	R^2	$(R^{13})_p$	$(R^{10})_p$
5	NO_2	1	CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
	H	1	CH_2CH_3	-	$CH_2COOt\text{-}Bu$	-	H
	OH	1	CH_2CH_3	-	$CH_2COOt\text{-}Bu$	-	H
	H	1	CH_2COOEt	-	$CH_2COOt\text{-}Bu$	-	H
	OH	1	CH_2COOEt	-	$CH_2COOt\text{-}Bu$	-	H
10	H	1	CH_2CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
	OH	1	CH_2CH_2COOH	-	$CH_2COOt\text{-}Bu$	-	H
	H	1	H	-	CH_2COOEt	-	H
	Cl	1	H	-	CH_2COOEt	-	H
	F	1	H	-	CH_2COOEt	-	H
15	CF_3	1	H	-	CH_2COOEt	-	H
	OH	1	H	-	CH_2COOEt	-	H
	NO_2	1	H	-	CH_2COOEt	-	H
	H	1	CH_3	-	CH_2COOEt	-	H
	Cl	1	CH_3	-	CH_2COOEt	-	H
20	F	1	CH_3	-	CH_2COOEt	-	H
	CF_3	1	CH_3	-	CH_2COOEt	-	H
	OH	1	CH_3	-	CH_2COOEt	-	H
	NO_2	1	CH_3	-	CH_2COOEt	-	H
	H	1	CH_2COOH	-	CH_2COOEt	-	H
25	Cl	1	CH_2COOH	-	CH_2COOEt	-	H
	F	1	CH_2COOH	-	CH_2COOEt	-	H
	CF_3	1	CH_2COOH	-	CH_2COOEt	-	H
	OH	1	CH_2COOH	-	CH_2COOEt	-	H
	NO_2	1	CH_2COOH	-	CH_2COOEt	-	H
30	H	1	CH_2CH_3	-	CH_2COOEt	-	H
	OH	1	CH_2CH_3	-	CH_2COOEt	-	H
	H	1	CH_2COOEt	-	CH_2COOEt	-	H
	OH	1	CH_2COOEt	-	CH_2COOEt	-	H
	H	1	CH_2CH_2COOH	-	CH_2COOEt	-	H
	OH	1	CH_2CH_2COOH	-	CH_2COOEt	-	H

TABLE 13

Compounds of the Formula



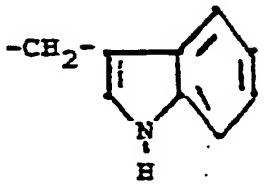
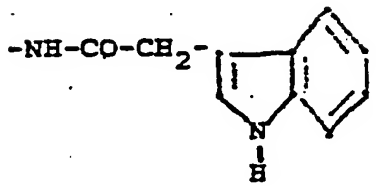
No.	R^a	R^1	R^3
577	F	$-CH_2-CF_3$	
586	F	H	
625	H	H	

TABLE 13 (Cont'd)

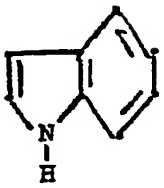
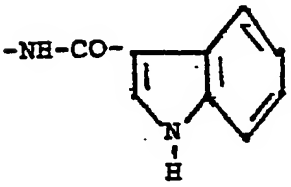
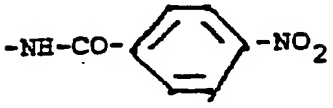
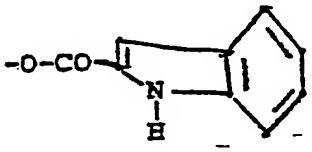
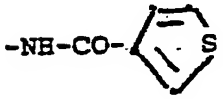
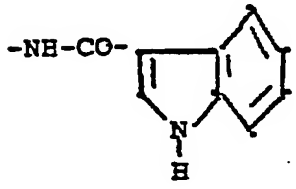
No.	R^a	R^1	R^3
643	F	$-(CH_2)_2-CN$	
648	F	H	
651	F	H	
652	H	H	
659	F	H	
665	H	H	

TABLE 13 (Cont'd)

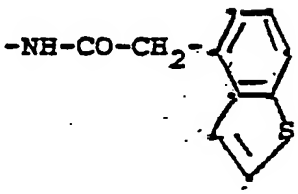
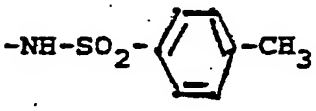
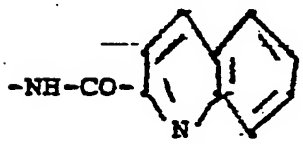
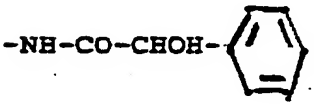
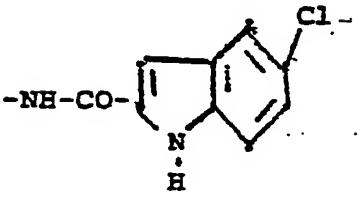
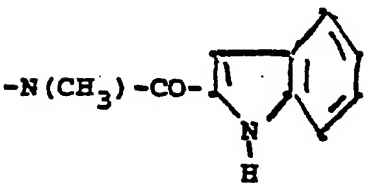
No.	R^a	R^1	R^3
666	F	H	
668	F	H	
676	F	H	
677	F	H	
678	F	H	
679	H	H	

TABLE 13 (Cont'd)

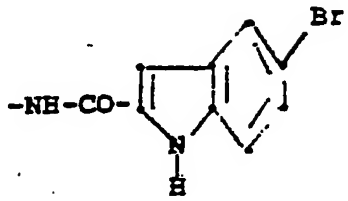
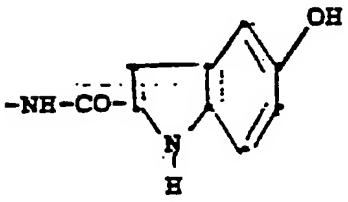
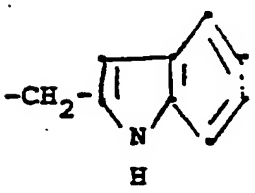
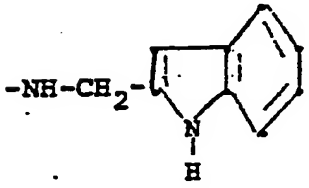
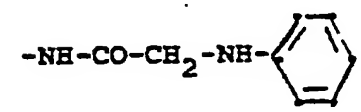
No.	R^a	R^1	R^3
686	F	H	
688	F	H	
690	F	$-CH_2-CO-NH_2$	
691	F	H	
692	F	H	

TABLE 13 (Cont'd)

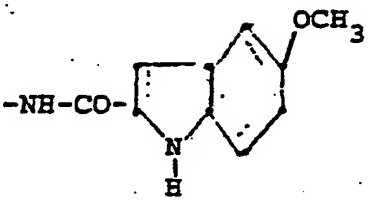
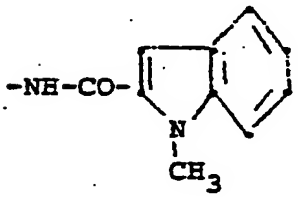
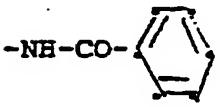
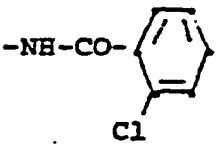
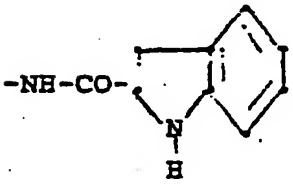
No.	R^a	R^1	R^3
694	F	H	
695	F	H	
716	H	H	
720	F	H	
722	H	H	

TABLE 13 (Cont'd)

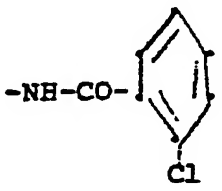
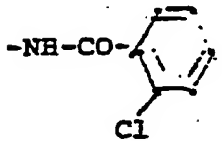
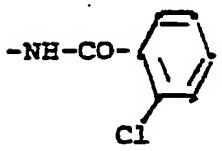
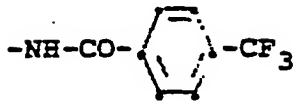
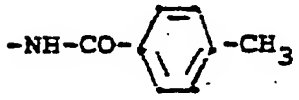
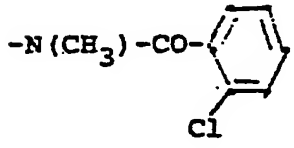
No.	R^a	R^1	R^3
724	H	H	
725	H	CH_3	 [(-)-enantiomer]
726	H	CH_3	 [(+)-enantiomer]
736	F	H	
737	F	H	
727	H	CH_3	

TABLE 13 (Cont'd)

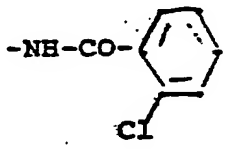
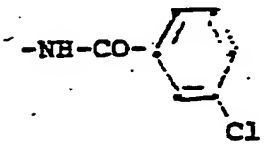
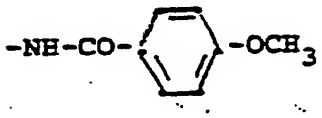
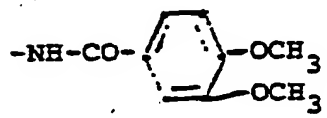
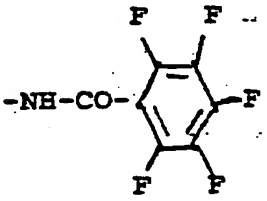
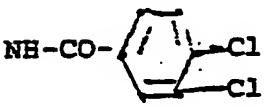
No.	R^a	R^1	R^3
728	H	CH_3	
740	H	H	
745	F	H	
752	F	H	
753	F	H	
755	H	H	

TABLE 13 (Cont'd)

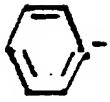
No.	R^a	R^1	R^3
761	F	CH_3	-NH-CO-  -Cl (N^4-oxide)
763	F	H	-NH-COO-CH_2- 
772	H	H	-NH-CO-  -SCH_3
779	F	-CO-  -Cl	-NH-CO-  -Cl
781	H	H	-NH-CO-  SCF_3
782	H	H	-NH-CO-  -CF_3
786	F	-CO-  -Cl	-O-CO-  -Cl

TABLE 13 (Cont'd)

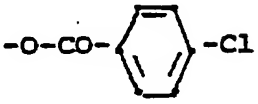
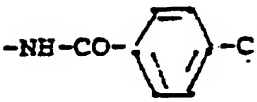
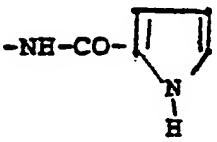
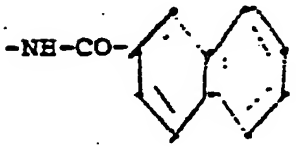
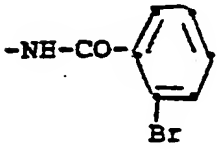
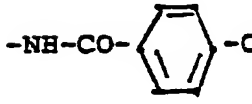
No.	R^a	R^1	R^3
787	F	H	
790	F	CH_3	 (+)enantiomer
791	F	H	
793	H	H	
794	F	CH_3	 (-)enantiomer
795	F	CH_3	 (+)enantiomer

TABLE 13 (Cont'd)

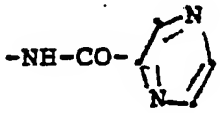
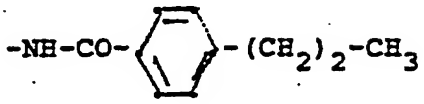
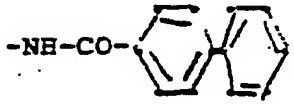
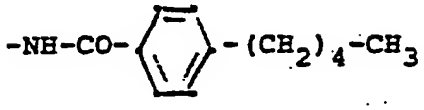
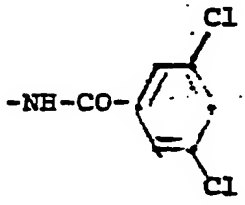
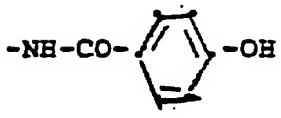
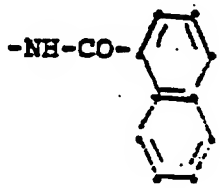
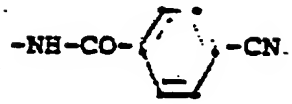
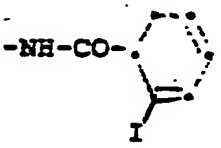
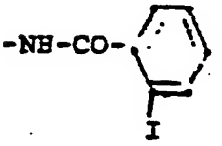
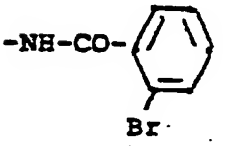
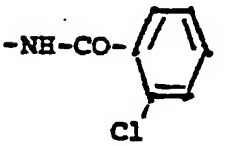
No.	R^a	R^1	R^3
796	H	H	
799	H	H	
800	H	H	
801	H	H	
802	H	H	
803	H	H	
804	H	H	

TABLE 13 (Cont'd)

No.	R^a	R^1	R^3	
805	H	H		
816	H	H		
825	F	CH_3		(+)enantiomer
827	F	CH_3		(-)enantiomer
829	F	CH_3		(+)enantiomer
830	F	CH_3		(+)enantiomer

Other compounds of Formula I are listed on the following table.

TABLE 14

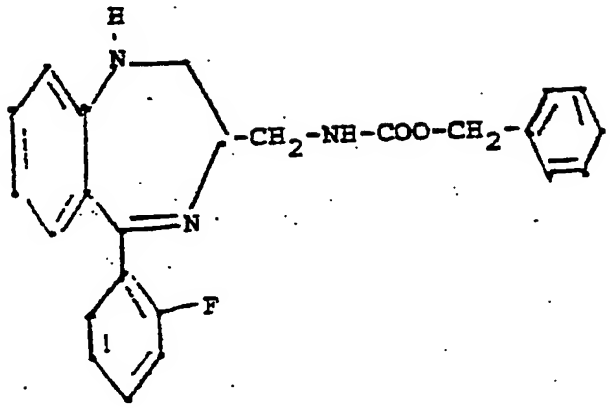
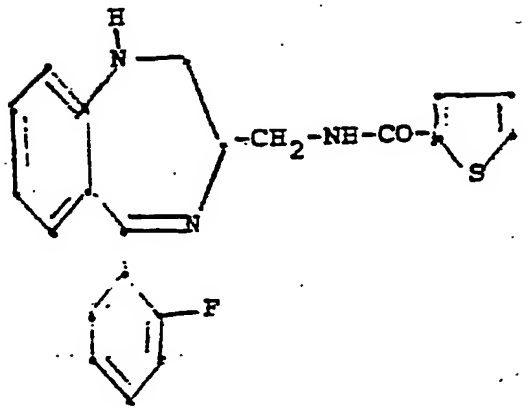
No.	Compound
632	
633	

TABLE 14 (Cont'd)

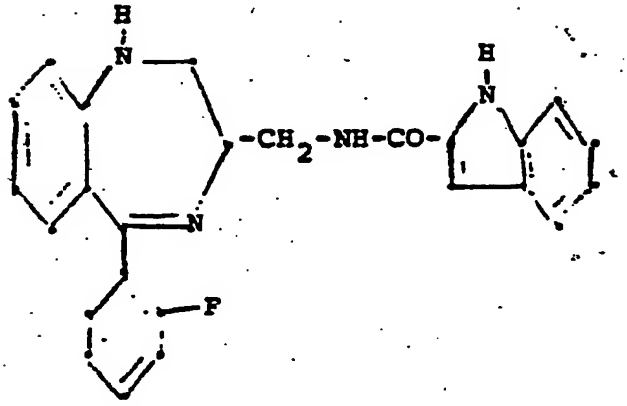
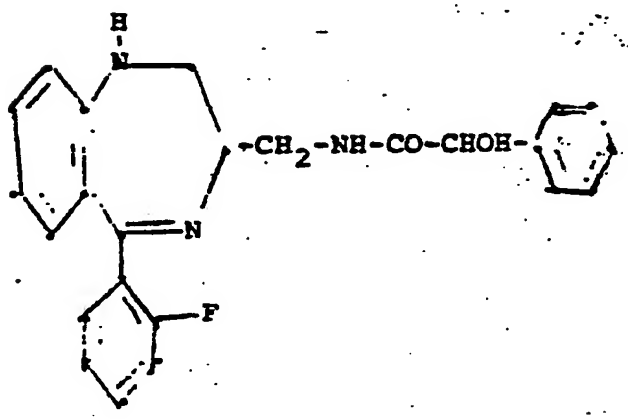
No.	Compound
636	
638	

TABLE 14 (Cont'd)

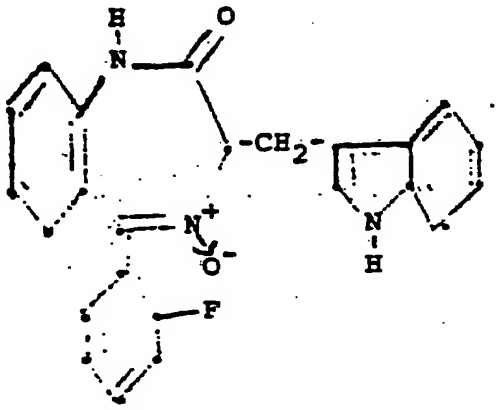
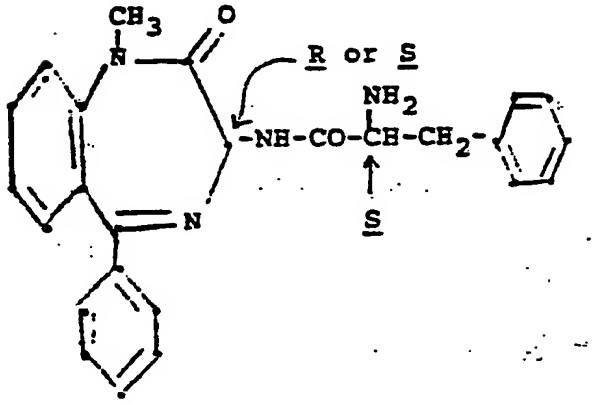
No.	Compound
646	
732	

TABLE 14 (Cont'd)

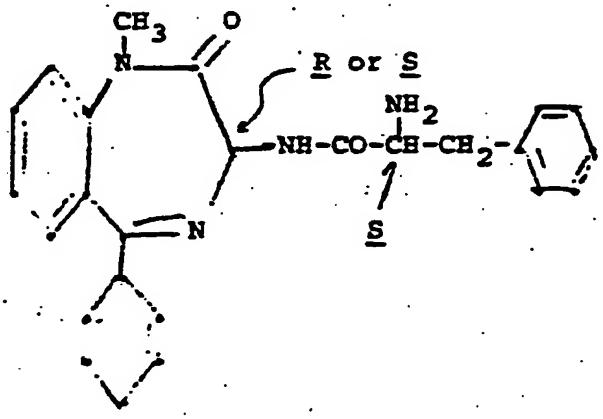
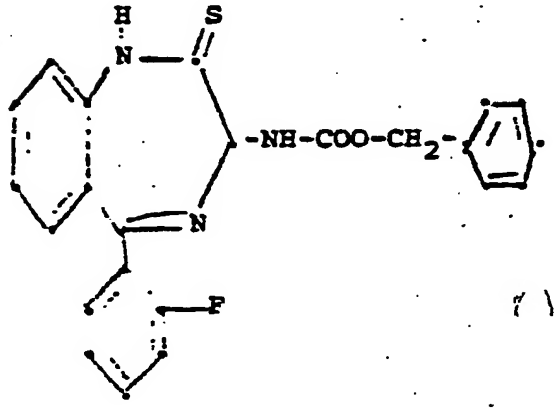
No.	Compound
733	
777	

TABLE 14 (Cont'd)

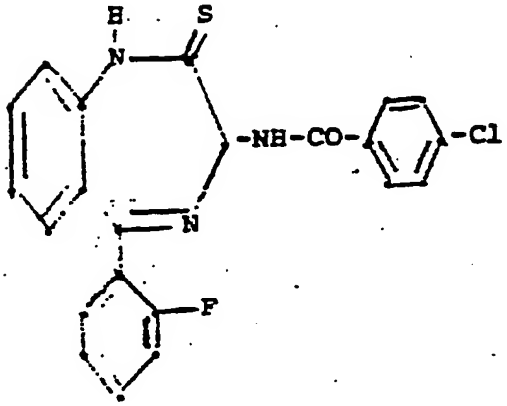
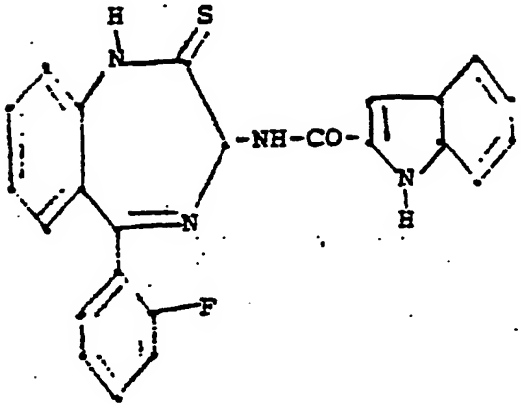
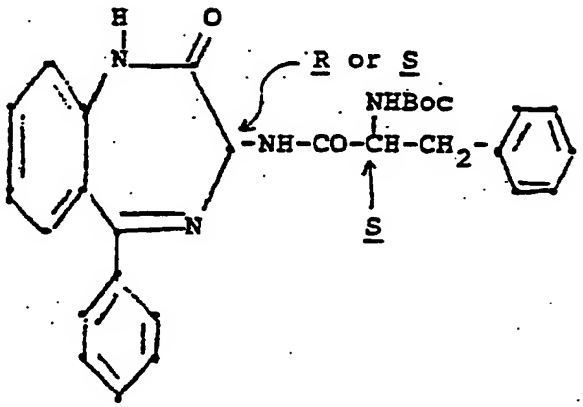
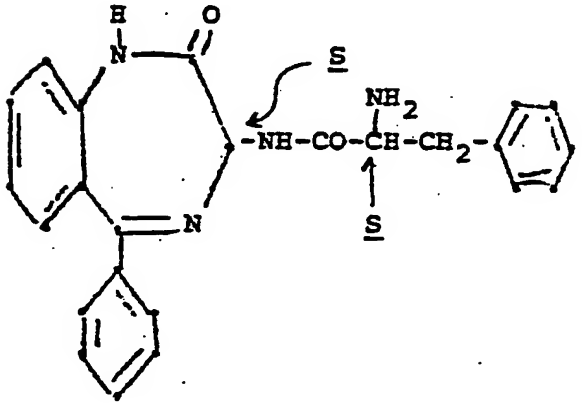
No.	Compound
808	
809	

TABLE 14 (Cont'd)

No.	Compound
826	
828	

The invention is further defined by reference to the following preparations and examples, which are intended to be illustrative and not limiting.

All temperatures are in degrees Celsius.

EXAMPLE 1

2-N-(N^{α}-Boc-D-tryptophanyl)amino-2'-fluorobenzophenone

2-Amino-2'-fluorobenzophenone (4 g, 18.6 mmole), Boc-D-tryptophan (5.65 g, 18.6 mmole) and dicyclohexylcarbodiimide (DCC) (18.6 ml of a 1M solution in methylene chloride, 18.6 mmole) were combined in 28 ml of dry tetrahydrofuran stirred in an ice bath. The mixture was allowed to warm to room temperature and stirred overnight. The solids were removed by filtration and the filtrate evaporated in vacuo. The residue was chromatographed on 9" (23 cm) of silica gel (230-400 mesh) in a 55 mm diameter column using 1L of each of methylene chloride and 2% and 3% (v/v) diethyl ether in methylene chloride.

The product fractions were combined and evaporated in vacuo. The residue was crystallized from diethyl ether and the resulting solid dried in vacuo at 40° for 20 hours: (m.p. 64-67°).

The compound showed a single component by thin layer chromatography (TLC) (R_f=0.36, silica gel plate eluted with 6% (v/v) diethyl ether in methylene chloride). The NMR spectrum was consistent with the title structure and verified the presence of Et_2O.

Anal. Calc'd for $C_{29}H_{28}FN_3O_4.Et_2O$:
C, 68.85; H, 6.65; N, 7.30.
Found: C, 69.25; H, 6.75; N, 7.30.

EXAMPLE 2

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one

2-N-(N^{α}-Boc-D-tryptophanyl)amino-2'-fluorobenzophenone (4.0 g=8.0 mmole) in 37 ml of ethyl acetate was stirred in an ice bath and saturated with hydrogen chloride gas for 20 minutes. The mixture was evaporated to dryness in vacuo to give 2-N-(D-tryptophanyl)amino-2'-fluorobenzophenone hydrochloride. The residue in 125 ml of methanol was treated with 30 ml of water and the pH of the mixture adjusted to 8.5-9.0 with 10% sodium hydroxide solution. The mixture was stirred at room temperature for three days.

The suspension was filtered and the resulting white solid dried in vacuo at 40° overnight: (m.p. 251-254°).

The compound showed a single component by thin layer chromatography (TLC) (R_f=0.59, silica gel plate eluted with 1:1 (v/v) diethyl ether/methylene chloride) and by HPLC (greater than 99%). The NMR spectrum was consistent with the title structure. The mass spectrum showed a molecular ion at m/e=383.

Anal. Calcd. for $C_{24}H_{18}FN_3O$:
C, 75.18; H, 4.73; N, 10.96.
Found: C, 74.88; H, 4.70, N, 10.65.

EXAMPLE 3

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one

2-Amino-2'-fluorobenzophenone (12.5 g=58 mmole) was stirred in 100 ml of dry tetrahydrofuran

in an ice bath. D-Tryptophan acid chloride hydrochloride (16 g = 62 mmole), slurried in 50 ml of tetrahydrofuran, was added over 10 minutes, and the mixture stirred 2 hours in the ice bath. The resulting solid was filtered, then added to 200 ml of methanol containing 200 ml of water. The pH was adjusted to 8.5-9.0 with 10% sodium hydroxide, the mixture was stirred for three days, then filtered. The solid was dried in vacuo at 40°.

EXAMPLE 4

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-[3'-(1'-methyl-indolyl)-methyl]-1-methyl-2H-1,4-benzodiazepin-2-one (A) and 1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl) methyl-1-methyl-2H-1,4-benzodiazepin-2-one (B)

A 1,3-Dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one (0.85 g, 2.2 mmole) and sodium hydride (0.11 g of a 50% suspension in mineral oil, 2.3 mmole) were stirred in 10 ml of dry, degassed dimethylformamide under nitrogen in an ice bath. After 40 minutes, methyl iodide (0.14 mL = 2.25 mmole) was added in one portion. The mixture was stirred for 1.5 hours at room temperature, then poured into 100 ml of water and extracted with methylene chloride (CH_2Cl_2) (3 x 30 mL). The CH_2Cl_2 layers were washed with water, dried over potassium carbonate, filtered and evaporated in vacuo. The residue was chromatographed on 9" (23 cm) of silica gel (250-400 mesh) in a 55 mm diameter column eluted with 4% (v/v) diethyl ether in CH_2Cl_2. The first product eluted was A which was obtained as a glass upon evaporation. The solid was dried in vacuo at room temperature: (m.p. 97-100°( )).

The compound showed a single component by thin layer chromatography (R_f=0.57, silica gel plate eluted with 10% (v/v) diethyl ether in CH_2Cl_2) and by HPLC (98%). The NMR spectrum was consistent with the title structure and verified the presence of CH_2Cl_2. The mass spectrum showed a molecular ion at m/e=411.

Anal. Calc'd. for $C_{26}H_{22}FN_3O \cdot 0.1\ CH_2Cl_2$
C, 74.64; H, 5.33, N, 10.01.
Found: C, 74.69; H, 5.32; N, 9.63.

B The second component eluted was the monomethyl compound B which was obtained as a foam (0.66 g) upon evaporation. Crystallization from hexane/CH_2Cl_2 gave analytical material; (m.p. 80-85°( )).

The compound showed a single component by thin layer chromatography (silica gel plates eluted with 4% (v/v) diethyl ether in CH_2Cl_2) and by HPLC (99%). The NMR spectrum was consistent with the title structure and verified the presence of CH_2Cl_2.

Anal. Calc'd for $C_{25}H_{20}FN_3O \cdot 0.75\ CH_2Cl_2$:
C, 67.06, H, 4.70; N, 9.11;
Found: C, 67.04; H, 4.81; N, 9.14.

EXAMPLE 5

7-Chloro-1,3-dihydro-3(R)-(3'-indolyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

2-Amino-5-chlorobenzophenone (1.2 g, 5.2 mmole) and D-tryptophan methyl ester hydrochloride (1.3 g, 5.1 mmole) were combined in dry pyridine (25 mL) and heated at reflux under nitrogen for 5 hrs.

The mixture was evaporated in vacuo and the residue washed twice with pH 6 buffer and dissolved in ethyl acetate (50 mL). The ethyl acetate solution was dried over sodium sulfate, filtered, and evaporated in vacuo to give an oil which was chromatographed on a 13 inch (33 cm) column of silica gel (230-400 mesh) in a 25 mm diameter column eluted with 20% (v/v) ether methylene choride. The product fractions were evaporated in vacuo to give the title compound as a white solid which was dried in vacuo at 100°: (m.p. 130-155°( )).

The compound showed a single spot by thin layer chromatography (R_f=0.36, silica gel plate eluted with 4:1 CH_2Cl_2/ether). The NMR spectrum was consistent with the title structure and verified the presence of ether. The compound was 99.8% pure by HPLC. The mass spectrum showed a molecular ion at m/e=399.

Anal. Calc'd for $C_{24}H_{18}ClN_3O \cdot 0.5C_4H_{10}O$:
C, 71.47; H, 5.31; N, 9.62; Cl, 8.12.
Found C, 71.62; H, 5.83; N, 9.47; Cl, 8.24.

EXAMPLE 6

1,3-Dihydro-3(R)-(3'-indolyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 1 was carried out using 2-aminobenzophenone (1.97 g, 0.01 mole), Boc-D-tryptophan (3.04 g, 0.01 mole) and DCC (10 mL of 1M solution in methylene chloride (CH_2Cl_2) in THF (15 mL). The crude product obtained after filtration and evaporation of the mixture was deprotected and cyclized by the procedure of Example 2. The mixture was evaporated in vacuo, combined

with water (50 mL) and extracted with chloroform (250 mL). The chloroform solution was hired over potassium carbonate, filtered, and evaporated to dryness in vacuo. Recrystallization from a mixture of acetone (50 mL) and ether (50 mL) gave a white solid which was dried in vacuo at 100°: (m.p. 260-263° (d)).

The compound showed a single spot by TLC (R_f=0.53, silica gel plate eluted with 1:1 CH_2Cl_2/ether). The NMR spectrum was consistent with the title structure and verified the presence of acetone. The compound was 99.6% pure by HPLC. The mass spectrum showed a molecular ion at m/e=365.

Anal. Calc'd for $C_{24}H_{19}N_3O \cdot 0.5C_3H_6O$:
C, 77.64, H, 5.62, N, 10.65.
Found: C, 77.34, H, 5.44, N, 10.87.

EXAMPLE 7

1,3-Dihydro-3(S)-[3'-(1'-methylindolyl)methyl]-1-methyl-5-methylthio-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-3(S)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one-5-thione (450 mg, 1.4 mmole) was suspended in 30 ml of toluene, 8 ml of tetrahydrofuran, and 15 ml of 40% sodium hydroxide solution. This mixture was treated with 203 mg (0.6 mmole) of tetra-n-butylammonium sulfate and 0.25 ml (4.0 mmole) of iodomethane and stirred rapidly at room temperature. After four hours the phases were separated and the aqueous layer extracted once with ethyl acetate. The combined organic extracts were washed with water (2 X 50 ml) and brine, then dried ($MgSO_4$) and concentrated in vacuo to afford a yellow oil. Preparative thick layer chromatography

(hexane-ethyl acetate 2:1 v/v) afforded the title compound as a white solid. R_f = 0.45 (2:1 hexane-ethyl acetate). The analytical sample was recrystallized from ethyl acetate-ether, m.p. 170°C; TLC, HPLC: 99% pure. Pmr ($CDCl_3$): according to theory (methyl proton resonate 2.46 ppm, 3.39 ppm, and 3.72 ppm respectively). MS (20 ev.): 363 (M^+), 184, 144.

Elemental Analysis: $C_{21}H_{21}N_3OS$

Calc'd. : N, 11.56; C, 69.39; H, 5.82.

Found: N, 11.47; C, 69.22; H, 6.04.

EXAMPLE 8

1,3-Dihydro-3(S)-(3'-indolyl)methyl-1-methyl-5-methyl-thio-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-3(S)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one-5-thione (450 mg, 1.4 mmole) was suspended in 30 ml of toluene, 8 ml of tetrahydrofuran, and 15 ml of 40% sodium hydroxide solution. The mixture was treated with 203 mg (0.6 mmole) of tetra-n-butylammonium sulfate and 0.25 ml (4.0 mmole) of iodomethane and stirred rapidly at room temperature. After four hours the phases were separated and the aqueous layer extracted once with ethyl acetate. The combined organic extracts were washed with water (2 X 50 ml) and brine, then dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil. Preparative thick layer chromatography (hexane-ethyl acetate 2:1 v/v) afforded the title compound as a white solid. R_f = 0.40 (2:1 hexane-ethyl acetate). The analytical sample was recrystallized from ethyl acetate-ether, m.p. 90-91°C. TLC, HPLC: 99% pure. Pmr ($CDCl_3$): according to

theory (methyl protons resonate at 2.45 ppm and 3.40 ppm, respectively). MS (20 ev): 349 (M^+), 302, 220, 130.

Elemental Analysis: $C_{20}H_{19}N_3OS$.

Calc'd. : N, 12.02; C, 68.74; H, 5.48.

Found: N, 12.10; C, 68.58; H, 5.71.

EXAMPLE 9

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-(3'-α-indolenyl) methyl-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one (120 mg, 0.31 mmole) was dissolved in 2 ml of trifluoroacetic acid. The resulting orange solution was treated with 0.5 ml (3.1 mmole) of triethylsilane and stirred rapidly at room temperature. After two hours, the reaction mixture was rotoevaporated to dryness and the residue was partitioned between water/ethyl acetate. The organic phase was washed with sodium bicarbonate solution (sat.), and brine, then dried ($MgSO_4$) and concentrated. The analytical sample was obtain via preparative thick layer chromatography on silica gel (1:1 hexane-ethyl acetate v/v, multiple elutions).

R_f = 0.38 (2:1 ethyl acetate-hexane).

Pmr ($CDCl_3$): in accord with theory.

MS (FAB): 386 (M+H).

Elemental Analysis: $C_{24}H_{20}FN_3O \cdot 0.4H_2O$

Calc'd. : N, 10.70; C, 73.41; H, 5.34.

Found: N, 10.50; C, 73.62; H, 5.45.

EXAMPLE 10

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-(3'-B-indolenyl) methyl-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one (120 mg, 0.31 mmole) was dissolved in 2 ml of trifluoroacetic acid. The resulting orange solution was treated with 0.5 ml (3.1 mmole) of triethylsilane and stirred rapidly at room temperature. After two hours, the reaction mixture was rotoevaporated to dryness and the residue was partitioned between water/ethyl acetate. The organic phase was washed with sodium bicarbonate solution (sat.), and brine, then dried ($MgSO_4$) and concentrated. The analytical sample was obtained *via* preparative thick layer chromatography on silica gel (1:1 hexane-ethyl acetate v/v, multiple elutions). R_f = 0.30 (2:1 ethyl acetate-hexane). Pmr ($CDCl_3$): in accord with theory. MS (FAB): 386 (M+H).

Elemental Analysis: $C_{24}H_{20}FN_3O \cdot 0.3H_2O$

Calc'd. : N, 10.75; C, 73.75; H, 5.31.

Found: N, 10.57; C, 73.86; H, 5.38.

EXAMPLE 11

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-thione

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one (6.98 g, 18.20 mmole) was refluxed with 4.41 g (10.92 mmole) of 2,4-bis-(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane in 100 ml of toluene for 1.5 hours. The solvent was removed *in vacuo* and the residue partitioned between ethylacetate and 10%

sodium hydroxide solution. The organic phase was washed with 10% sodium hydroxide (3 X 50 ml) and brine, then dried ($MgSO_4$) and rotoevaporated to give an orange oil (10 g). Plug filtration of the crude product through silica gel (100 g) afforded a solid which was recrystallized from ether to afford the analytical sample.

m.p. 147-148°C.

Pmr: according to theory.

EXAMPLE 12

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepine

To a solution of 1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-thione (178 mg, 0.44 mmole) in 20 ml of absolute ethanol was added at room temperature one spatula of moist (ethanol) Raney-nickel catalyst (freshly prepared according to Fieser and Fieser, "Reagents for Organic Synthesis", Vol. I, p. 729, John Wiley & Sons., Inc. N.Y., 1967). The resulting suspension was protected from moisture and stirred rapidly for one hour. The reaction mixture was filtered and the filtrate concentrated to give 150 mg of a yellow oil. Purification via silica gel chromatography (chloroform-methanol-ammonia 95:5:0.5 v/v) afforded the analytical sample.

TLC, HPLC: confirmed purity.

MS (20 ev): 369 (M^+), 239, 212, 130, 83.

Pmr ($CDCl_3$): according to theory.

Elemental Analysis: $C_{24}H_{20}FN_3 \cdot 0.07\ CHCl_3$.

Calc'd. : N, 11.12; C, 76.52; H, 5.35.

Found: N, 10.90; C, 76.66; H, 5.59.

EXAMPLE 13

7-Chloro-1,3-dihydro-3(R)-benzyl-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 1 was carried out using 2-amino-5-chlorobenzophenone (2.32 gm, 0.01 mol), Boc-D-Phenylalanine (2.65 gm, 0.01 mol), and DCC (10 ml of 1.0 M solution in CH_2Cl_2) in CH_2Cl_2 (10 ml). After filtration and evaporation, the crude solid was deprotected and cyclized by the procedure of Example 2. After stirring 5 days, the mixture was evaporated in vacuo, treated with H_2O (50 ml), and extracted with EtoAc (2 x 100 ml). The combined organic extracts were washed with brine (50 ml), dried over $MgSO_4$, filtered and evaporated to dryness in vacuo. Chromatography on silica gel eluted with 7.5% (v/v) Et_2O in CH_2Cl_2 gave a white foam which was crystallized from Et_2O. The solid was dried in vacuo at 65°C: (m.p. 154-7°C).

The compound showed a single spot by TLC (R_f=0.32, silica gel plate eluted with 10% (v/v) Et_2O in CH_2Cl_2). The NMR spectrum was consistent with the title structure. The compound was 100% pure by HPLC.

Anal. Calc'd for $C_{22}H_{17}ClN_2O$:
C, 73.23; H, 4.75; N, 7.76; Cl, 9.83.
Found: C, 73.59; H, 4.78; N, 7.95; Cl, 10.03.

EXAMPLE 14

7-Chloro-1,3-dihydro-3(R)-(2-methyl-1-propyl)-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 1 was carried out using 2-amino-5-chlorobenzophenone (2.32 gm, 0.01 ml), Boc-D-Leucine monohydrate (2.49 gm, 0.01 mol),

and DCC (10 ml of 1.0 M solution in CH_2Cl_2) in CH_2Cl_2 (25 ml). Filtration, concentration in vacuo and chromatography (silica gel, 5% (v/v) Et_2O in CH_2Cl_2) gave a yellow oil which was deprotected and cyclized by the procedure of Example 2. After stirring 48 h, the mixture was evaporated in vacuo, treated with H_2O (50 ml), and extracted with EtOAc (2 x 200 ml). The combined organic extracts were washed with brine (50 ml), dried over $MgSO_4$, filtered, and evaporated to dryness in vacuo. Chromatography (silica gel, 7.5% (v/v) Et_2O in CH_2Cl_2) of the crude product gave a white foam which was crystallized from Et_2O. The solid was dried in vacuo at 65°C: (m.p. 156-60°C).

The compound showed a single spot by TLC (R_f=0.38, silica gel plate, 10% (v/v) Et_2O in CH_2Cl_2). The NMR spectrum was consistent with the title structure. The compound was 100% pure by HPLC.

Anal. Calc'd for $C_{19}H_{19}ClN_2O$:
C, 69.82; H, 5.86; N, 8.57; Cl, 10.85.
Found: C, 69.81; H, 5.84; N, 8.71; Cl, 11.20.

EXAMPLE 15

3(R)-Benzyloxymethyl-7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 1 was carried out using 2-amino-5-chlorobenzophenone (2.32 gm, 0.01 mol), N-Boc-O-Benzyl-D-serine (2.95 gm, 0.01 mol), and DCC (10 ml of 1.0 M solution in CH_2Cl_2) in CH_2Cl_2 (10 ml). Filtration, concentration in vacuo and chromatography (silica gel, CH_2Cl_2) gave a colorless oil which was deprotected and

cyclized by the procedure of Example 2. After stirring 5 days, the mixture was evaporated in vacuo, treated with H_2O (50 ml), and extracted with EtOAc (2 x 100 ml). The combined organic extracts were washed with brine (50 ml), dried over $MgSO_4$, filtered, and evaporated to dryness in vacuo. Chromatography (silica gel, 75% (v/v) Et_2O in CH_2Cl_2) of the crude product gave a white foam which was crystallized from Et_2O. The solid was dried in vacuo at 65°C: (m.p. 113-5°C).

The compound showed a single spot by TLC (R_f=0.27, silica gel plate, 10% (v/v) Et_2O in CH_2Cl_2). The NMR spectrum was consistent with the title structure and verified the presence of Et_2O and H_2O. The compound was 100% pure by HPLC.

Anal. Calc'd for $C_{23}H_{19}ClN_2O_2$·0.1 $C_4H_{10}O$·0.25 H_2O:
C, 69.78; H, 5.13; N, 6.96; Cl, 8.80.
Found: C, 69.53; H, 5.17; N, 6.99; Cl, 8.98.

EXAMPLE 16

7-Chloro-1,3-dihydro-3(R)-(4-benzyloxybenzyl)-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 1 was carried out using 2-amino-5-chlorobenzophenone (2.32 gm, 0.01 mol), N-Boc-O-Benzyl-D-Tyrosine (3.71 gm, 0.01 mol), and DCC (10 ml of 1.0 M solution in CH_2Cl_2) in CH_2Cl_2 (10 ml). After filtration and evaporation, the crude solid was deprotected and cyclized by the procedure of Example 2. After stirring 5 days, the mixture was evaporated in vacuo, treated with H_2O (75 ml), and extracted with EtOAc (2 x 125 ml). The combined organic extracts were washed with brine (50 ml), dried over $MgSO_4$,

filtered, and evaporated to dryness in vacuo. Chromatography (silica gel, 7.5% (v/v) Et_2O in CH_2Cl_2) of the crude product gave a white foam which was dried at 69°C in vacuo: (m.p. 97-101°C).

The compound showed a single spot by TLC (R_f=0.37, silica gel plate, 10% (v/v) Et_2O in CH_2Cl_2). The NMR spectrum was consistent with the title structure. The compound was greater than 99.5% pure by HPLC.

Anal. Calc'd for $C_{29}H_{23}ClN_2O_2$:
C, 74.59; H, 4.97; N, 6.00.
Found: C, 74.52; H, 4.78; N, 6.01.

EXAMPLE 17

7-Chloro-1,3-dihydro-3(RS)-(1-naphthyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 1 was carried out using 2-amino-5-chlorobenzophenone (845 mg, 3.65 mmol), N-Boc-α-DL-naphthylalanine (1.15 gm, 3.65 mmol), and DCC (3.65 ml of 1.0 M solution in CH_2Cl_2) in THF (5 ml). Filtration, concentration in vacuo and chromatography (silica gel, 1% (v/v) Et_2O in CH_2Cl_2) gave a light yellow foam which was deprotected and cyclized by the procedure of Example 2. After stirring 14 days, the mixture was evaporated in vacuo, treated with H_2O (25 ml), and extracted with CH_2Cl_2 (2 x 50 ml). The combined organic extracts were washed with brine (25 ml), dried over $MgSO_4$, filtered, and evaporated to dryness in vacuo. Chromatography (silica gel, 3% (v/v) Et_2O in CH_2Cl_2) of the crude product gave a white foam which was crystallized from hexane. The solid was dried in vacuo at 100°C: (m.p. 180-2°C).

The compound showed a single spot by TLC (R_f=0.36, silica gel plate, 10% (v/v) Et_2O in CH_2Cl_2). The NMR spectrum was consistent with the title structure. The compound was greater than 99.9% pure by HPLC.

Anal. Calc'd for $C_{26}H_{19}ClN_2O$:
C, 76.00; H, 4.66; H, 6.82; Cl, 8.63.
Found: C, 75.99; H, 4.68; N, 6.65; Cl, 8.76.

EXAMPLE 18

7-Chloro-1,3-dihydro-3(RS)-(2-naphthyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 1 was carried out using 2-amino-5-chlorobenzophenone (845 mg, 3.65 mmol), N-Boc-β-DL-naphthylalanine (1.15 gm, 3.65 mmol), and DCC (3.65 ml of 1.0 M solution in CH_2Cl_2) in THF (5 ml). Filtration, concentration in vacuo and chromatography (silica gel, 1% (v/v) Et_2O in CH_2Cl_2) gave a foam which was deprotected and cyclized by the procedure of Example 2. After stirring 24 hours, the mixture was evaporated in vacuo, treated with H_2O (25 ml), and extracted with EtOAc (2 x 50 ml). The combined organic extracts were washed with brine (25 ml), dried over $MgSO_4$, filtered, and evaporated to dryness in vacuo. Chromatography (silica gel, 5% (v/v) Et_2O in CH_2Cl_2) of the crude product gave a foam which was crystallized from Et_2O/hexane. The solid was dried in vacuo at 100°C: (m.p. 140-2°C).

The compound showed a single spot by TLC (R_f=0.38, silica gel plate, 10% (v/v) Et_2O in CH_2Cl_2). The NMR spectrum was consistent with the title structure. The compound was greater than 99.7% pure by HPLC.

Anal. Calc'd for $C_{26}H_{19}ClN_2O$:
C, 76.00; H, 4.66; N, 6.82; Cl, 8.63.
Found: C, 75.77; H, 4.68; N, 6.77; Cl, 8.87.

EXAMPLE 19

1,3-Dihydro-5-(2-fluorophenyl)-3(RS)-(2-thienyl)methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 1 was carried out using 2-amino-2'-fluorobenzophenone (1.26 gm, 5.86 mmol), N-Boc-ß-(2-thienyl)-DL-alanine (1.75 gm, 6.45 mmol), and DCC (6.45 ml of 1.0M solution in CH_2Cl_2) in CH_2Cl_2 (25 ml). Filtration, concentration in vacuo and flash chromatography (silica gel, 1% (v/v) Et_2O in CH_2Cl_2) gave a white foam which was deprotected and cyclized by the procedure of Example 2. After stirring 3 days, the mixture was evaporated in vacuo, treated with H_2O (50 ml) and extracted with EtOAc (2 x 100 ml). The combined organic extracts were washed with brine (50 ml), dried over $MgSO_4$, filtered, and evaporated to dryness in vacuo. The resulting foam was crystallized from Et_2O to give the title compound as a white solid. The solid was dried in vacuo at 65°C: (m.p. 189-91°C).

The compound showed a single spot by TLC (R_f=0.54, silica gel plate, 20% (v/v) Et_2O in CH_2Cl_2).

The NMR spectrum was consistent with the title structure. The compound was greater than 97.9% pure by HPLC.

Anal. Calc'd for $C_{20}H_{15}FN_2OS$:
C, 68.55; H, 4.32; N, 8.00.
Found: C, 68.74; H, 4.47; N, 8.02.

EXAMPLE 20

1,3-Dihydro-5-(2-fluorophenyl)-3(RS)-(3-thienyl)-2H-1,4-benzodiazepin-2-one

The procedure of Example 1 was carried out using 2-amino-2'-fluorobenzophenone (1.59 g, 7.40 mmol), DL-α-Boc-amino-3-thiopheneacetic acid (2.0 gm, 7.77 mmol), and DCC (7.77 ml of 1.0M solution in CH_2Cl_2) in CH_2Cl_2 (15 ml). Filtration, concentration in vacuo and chromatography (silica gel, 3% (v/v) Et_2O in CH_2Cl_2) gave a white foam which was deprotected (HCl/EtoAc, 0°) and cyclized by heating (70°C oil bath) in MeOH for 48 hours. The solvent was removed in vacuo and the residue crystallized from Et_2O. The compound was dried in vacuo at 65°C: (m.p. 219-23°C).

The compound showed a single spot by TLC (R_f=0.24, silica gel plate, 30% (v/v) EtOAc in hexane). The NMR spectrum was consistent with the title structure. The compound was greater than 98.5% pure by HPLC.

Anal. Calc'd for $C_{19}H_{13}FN_2OS$:
C, 67.84; H, 3.90; N, 8.33.
Found: C, 67.75; H, 4.13; N, 7.98.

EXAMPLE 21

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-[3'-β-(1'-t-Boc-L-leucyl)-indolenyl]methyl-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-(3'-β-indolenyl)methyl-2H-1,4-benzodiazepin-2-one (100 mg, 0.259 mmol), N-Boc-L-Leucine monohydrate (64.7 mg, 0.259 mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC, 49.8 mg, 0.259 mmol), and 1-hydroxybenzotriazole hydrate (HBT, 35.0

mg, 0.259 mmol) were combined in freshly degassed dimethylformamide (DMF, 2 ml) and stirred at room temperature. The pH of the solution was adjusted to 9.0-9.5 with triethylamine (0.108 ml, 0.777 mmol) and stirring was continued for 24 hours. The mixture was evaporated in vacuo, treated with 10% Na_2CO_3 (aq) (20 ml) and extracted with EtOAc (2 x 30 ml). The combined extracts were washed with H_2O (20 ml) and brine (20 ml), dried over $MgSO_4$, filtered, and evaporated to dryness in vacuo. The residue was chromatographed (silica gel, 30% (v/v) EtOAc in hexane) to give the title compound as a foam. The foam was dried in vacuo at 65°C: (m.p. 118-30°C).

The compound showed a single spot by TLC (R_f=0.38, silica gel plate, 40% (v/v) EtOAc in hexane). The NMR spectrum was consistent with the title structure and verified the presence of hexane. The compound was greater than 97% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 598.

Anal. Calc'd for $C_{35}H_{39}FN_4O_4 \cdot 1/3C_6H_{14}$:
C, 70.83; H, 7.02; N, 8.93.
Found: C, 70.93; H, 6.88; N, 8.94.

EXAMPLE 22

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-[3'-8-(1'-t-Boc-D-leucyl)-indolenyl]methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 21 was carried out using the same reagents and amounts except N-Boc-D-leucine monohydrate was substituted for N-Boc-L-leucine monohydrate. After 24 hours a second portion of Boc-D-Leucine monohydrate (32 mg, 0.129 mmol), EDC (25 mg, 0.130 mmol), and HBT (17.5 mg; 0.130 mmol) was added and the pH readjusted to

9.0-9.5 with Et_3N. The reaction was worked up as in Example 21, and the title compound was obtained as a foam. This was dried in vacuo at 65°C: (m.p. 135-48°C).

The compound showed a single spot by TLC (R_f=0.37, silica gel plate, 40% (v/v) EtOAc in hexane). The NMR spectrum was consistent with the title structure. The compound was 87.5% pure by HPLC. Anal. Calc'd for $C_{35}H_{39}FN_4O_4$:

C, 70.21; H, 6.57; N, 9.36.

Found: C, 70.25; H, 6.89; N, 9.53.

EXAMPLE 23

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-[3'-α-(1'-t-Boc-L-leucyl)-indolenyl]methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 21 was carried out using the same reagents and quantities except 1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-α-indolenyl) methyl-2H-1,4-benzodiazepin-2-one was substituted for the 3'-ß isomer. After 24 hours the reaction was worked up in the same manner and the title compound was obtained as a foam. This was dried in vacuo at 65°C: (m.p. 130-48°C).

The compound showed a single spot by TLC (R_f=0.39, silica gel plate, 40% (v/v) EtOAc in hexane). The NMR spectrum was consistent with the title compound. The compound was 91% pure by HPLC. Anal. Calc'd for $C_{35}H_{39}FN_4O_4$:

C, 70.21; H, 6.57; N, 9.36.

Found: C, 70.54; H, 6.98; N, 9.39.

EXAMPLE 24

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-[3'-α-(1'-t-Boc-D-leucyl)-indolenyl]methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 23 was carried out using the same reagents and quantities except Boc-D-Leucine was substituted for Boc-L-Leucine. After 24 hours the reaction was worked up in the same manner and the title compound was obtained as a white foam. This was dried in vacuo at 65°C: (m.p. 130-145°C).

The compound showed a single spot by TLC (R_f=0.39, silica gel plate, 40% (v/v) EtOAc in hexane). The NMR spectrum was consistent with the title structure. The compound was 95.1% pure by HPLC.

Anal. Calc'd for $C_{35}H_{39}FN_4O_4$:
C, 70.21; H, 6.57; N, 9.36.
Found: C, 70.31; H, 6.81; N, 9.67.

EXAMPLE 25

7-Chloro-1,3,4,5-tetrahydro-3(R)-(3'-indolyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

7-Chloro-1,3,dihydro-3(R)-(3'-indolyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one etherate (240 mg, 0.506 mmol) was dissolved in acetic acid (10 ml) and cooled to 10°C. To the yellow solution was added sodium cyanoborohydride (63.6 mg, 1.01 mmol) all at once. After stirring 15 minutes at 10°C, the reaction was diluted with H_2O (10 ml), basified with sat'd Na_2CO_3 (aq.), and extracted with EtOAc (2 x 25 ml). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness in vacuo. The residue was chromatographed (silica gel, 900/10/1/1 (v/v/v/v) of

CH_2Cl_2/MeOH/H_2O/HoAc) and the product fractions evaporated to dryness in vacuo. The residue was dissolved in absolute ethanol, filtered, and treated with 5.37 M HCl in ethanol until the solution was acidic. The product crystallized as fine white needles which were dried in vacuo at 82°C: (m.p. 198-204°C).

The compound showed a single spot by TLC (R_f=0.35, silica gel plate, 300/10/1/1 (v/v/v/v) CH_2Cl_2/MeOH/H_2O/HoAc). The NMR spectrum was consistent with the title structure and verified the presence of H_2O. The mass spectrum showed a molecular ion at m/e = 401.

Anal. Calc'd for $C_{24}H_{20}ClN_3O \cdot HCl \cdot 0.75H_2O$:
C, 63.79; H, 5.02; N, 9.30; Cl, 15.69.
Found: C, 63.59; H, 4.94; N, 9.39; Cl, 15.32.

EXAMPLE 26

7-Chloro-1,3,4,5-tetrahydro-3(S)-(3'-indolyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

7-Chloro-1,3-dihydro-3(S)-(3'-indolyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (300 mg, 0.750 mmol) was dissolved in acetic acid (10 ml) and cooled to 10°C. To the yellow solution was added sodium cyanoborohydride (63.6 mg, 1.01 mmol) all at once. After stirring 15 minutes at 10°C, the reaction was diluted with H_2O (10 ml), basified with sat'd Na_2CO_3(aq.), and extracted with EtOAc (2 x 25 ml). The combined organic extracts were washed with brine (10 ml), dried over $MgSO_4$, filtered, and evaporated to dryness in vacuo. The crude residue was dissolved in absolute ethanol (3 ml), filtered, and treated with 5.37M ethanolic HCl until the

solution was acidic. The product crystallized as fine white needles which were dried in vacuo at 82°C: (m.p. 198-204°C).

The compound showed a single spot by TLC (R_f=0.30, silica gel plate, 300/10/1/1 (v/v/v/v) of CH_2Cl_2/MeOH/H_2O/HoAc). The NMR spectrum was consistent with the title structure and verified the presence of H_2O and ethanol.

Anal. Calc'd for $C_{24}H_{20}ClN_3O \cdot HCl \cdot 0.5\ H_2O.0.25\ C_2H_5OH$:

C, 64.12; H, 5.16; N, 9.16; Cl, 15.45.

Found: C, 63.91; H, 5.02; N, 9.01; Cl, 15.36.

EXAMPLE 27

4-(p-Chlorobenzoyl)-5-(2-fluorophenyl)-3(R)-[3'-(1'-methylindolyl)-methyl]-1-methyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (A) and 4-acetyl-5-(2-fluorophenyl)-3(R)-[3'-(1'-methylindolyl)-methyl]-1-methyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one (B)

The procedure of Example 25 was carried out using 1,3-dihydro-5-(2-fluorophenyl)-3(R)-[3'-(1'-methylindolyl)-methyl]-1-methyl-2H-1,4-benzodiazepin-2-one (1.0 gm, 2.43 mmol) and sodium cyanoborohydride (305 mg, 4.86 mmol) in glacial acetic acid (4 ml). The crude reduction product obtained upon evaporation of the EtOAc extracts was used without further purification.

A The crude reduction product (200 mg, 0.484 mmol) was partitioned between CH_2Cl_2 (6 ml) and H_2O (5 ml) and cooled to 0°C. 1N NaOH (0.73 ml) was added, followed by p-chlorobenzoyl chloride (.092 ml, 0.726 mmol). After 24 hours at ambient

temperature, a second portion of 1N NaOH (0.50 ml) and p-chlorobenzoyl chloride (.045 ml, 0.354 mmol) was added, and after 24 hours a third portion of 1N NaOH (50 ml) and p-chlorobenzoylchloride (.045 ml, 0.354 mmol) was added. After another 24 hours, the mixture was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers were washed with 10% $NaHCO_3$ (10 ml), H_2O (10 ml), and brine (10 ml), dried over $MgSO_4$, filtered, and evaporated *in vacuo*. Chromatography (silica gel, 5% (v/v) Et_2O in CH_2Cl_2) of the crude residue gave a foam which was crystallized from Et_2O. The compound was dried *in vacuo* at 78°C: (m.p. 237-43°C).

Anal. Calc'd for $C_{33}H_{27}FClN_3O_2.0.05\ Et_2O$:
C, 71.75; H, 4.99; N, 7.56; Cl, 6.38.
Found: C, 71.84; H, 5.28; N, 7.92; Cl, 6.63.

The compound showed a single spot by TLC (R_f=0.50, silica gel plate, 4% (v/v) Et_2O in CH_2Cl_2). The NMR spectrum was consistent with the title structure and verified the presence of Et_2O. The compound was greater than 99% pure by HPLC.

B: The crude reduction product (200 mg, 0.484 mmol) was dissolved in CH_2Cl_2 (10 ml) and 3 portions of acetyl chloride (each 0.026 ml, 0.363 mmol) and triethylamine (0.35 ml, 0.363 mmol) were added at 3 hour intervals. Water (2 ml) was then added and the mixture was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers, were washed with 10% Na_2CO_3 (aq.) (10 ml), H_2O (10 ml) and brine (10 ml), dried over $MgSO_4$, filtered, and evaporated *in vacuo*. Chromatography (silica gel,

5% (v/v) Et_2O in CH_2Cl_2) of the crude residue gave a white foam which was crystallized from Et_2O. The compound was dried in vacuo at 78°C: (m.p. 214-216.5°C).

The compound showed a single spot by TLC (R_f=0.41, silica gel plate, 15% (v/v) Et_2O in CH_2Cl_2). The NMR spectrum was consistent with the title structure. The compound was greater than 99.5% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 455.

Anal. Calc'd for $C_{28}H_{26}FN_3O_2$:
C, 73.82; H, 5.75; N, 9.23.
Found: C, 73.62; H, 5.93; N, 9.22.

EXAMPLE 28

7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 1 was carried out using 2-amino-2',5-dichlorobenzophenone (2.66 g, 0.01 mole), Boc-D-tryptophan (3.04 g, 0.01 mole), and DCC (10 ml of 1 M solution in methylene chloride) in THF (15 ml). The crude product obtained after filtration and evaporation of the mixture was chromatographed on silica gel (230-400 mesh, 9 inch (23 cm) column 55 mm diameter), using methylene chloride followed by 5% (v/v) ether/methylene chloride. The product fractions were evaporated in vacuo to give the product as a foam. This material was deprotected and cyclized using the procedure of Example 2. The cyclization in this case required 15 days. At the end of this time the mixture was evaporated in vacuo, treated with water (10 ml), and extracted with methylene chloride (3 x 50 ml). The methylene

chloride layers were dried over potassium carbonate, filtered, and evaporated in vacuo to give the crude product as a foam. This material was chromatographed on silica gel (230-400 mesh, 8 inch (20 cm) column, 25 mm diameter, elution with methylene chloride followed by 10% (v/v) ether/methylene chloride). The product fractions were evaporated in vacuo and the residue crystallized from ether by addition of cyclohexane. The title compound was obtained as a white solid which was dried in vacuo at 80°: (mp 140-170° (d)).

The compound showed a single spot by TLC (R_f = 0.61, silica gel plate eluted with 1:1 (v/v) ether/methylene chloride). The NMR spectrum was consistent with the title structure. The mass spectrum showed a molecular ion at m/e = 433. The compound was 98% pure by HPLC.

Analysis Calc'd for $C_{24}H_{17}Cl_2N_3O$:
C, 66.37; H, 3.94; N, 9.68:
Found: C, 66.70; H, 4.05; N, 9.61.

EXAMPLE 29

1,3-Dihydro-3(R)-(3'-indolyl)methyl-5-methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 1 was carried out using 2-aminobenzophenone (1.35 g, 0.01 mole), Boc-D-tryptophan (3.04 g, 0.01 mole), and DCC (10 ml of 1M solution in methylene chloride) in THF (15 ml). The mixture was filtered, evaporated in vacuo and the residue chromatographed on silica gel (230-400 mesh, 9 inch (23 cm) column, 55 mm diameter) eluted with methylene chloride followed by 5%, 7-1/2% and 8% (v/v) ether/methylene chloride. The product

fractions were evaporated in vacuo and the residue was deprotected and cyclized by the procedure of Example 2. The cyclization required seven days. The mixture was evaporated in vacuo and partitioned between water and methylene chloride. The methylene chloride layers were washed twice with water, dried over magnesium sulfate, filtered and evaporated in vacuo. The residue was chromatographed on silica gel (230-400 mesh, 11 inch (28 cm) column, 25 mm diameter, 1:1 and 2:1 (v/v) ether/methylene chloride elution). The product fractions were evaporated in vacuo to provide the title compound: (mp 185-190°). The compound was dried in vacuum at 100° overnight.

The compound showed a single spot by TLC (R_f=0.29, silica gel plate eluted with 1:1 (v/v) ether/methylene chloride). The NMR spectrum was consistent with the title structure. The mass spectrum showed a molecular ion at m/e=303. The compound was 95.6% pure by HPLC.

Analysis Calc'd for: $C_{19}H_{17}N_3O \cdot 0.1H_2O$:
C, 74.78; H, 5.68; N, 13.78;
Found: C, 74.60; H, 6.06; N, 13.74.

EXAMPLE 30

1-Benzyl-7-chloro-1,3-dihydro-3(R)-(3'-indolyl) methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 4 was carried out using 7-chloro-1,3-dihydro-3(R)-(3'-indolyl)-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one etherate (0.1 g, 0.22 mmole) in place of 1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one, and 50% sodium hydride in mineral oil (0.015 g, 0.31 mmole) in dry DMF (2 ml). In place of

methyl iodide, benzyl bromide (0.058 g, 0.34 mmole) was added to the mixture. Chromatography on a 6 inch (15 cm), 15 mm diameter silica gel column with 5% (v/v) ether/methylene chloride elution and evaporation of the product fractions gave a residue which was recrystallized from cyclohexane to provide the title compound which was dried in vacuo at 60°: (mp ca. 80° (indistinct)).

The compound showed a single spot by TLC (R_f=0.66, silica gel plate eluted with 10% (v/v) ether/methylene chloride). The NMR spectrum was consistent with the title structure and verified the presence of approximately 1/2 mole of cyclohexane. The compound was 100% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 489.

Analysis Calc'd for: $C_{31}H_{24}ClN_3O \cdot 0.5C_6H_{12}$:
C, 76.74; H, 5.68; N, 7.90; Cl, 6.66;
Found: C, 76.83; H, 5.71; N, 7.79; Cl, 6.72.

EXAMPLE 31

7-Chloro-1,3-Dihydro-3(R)-(3'-indolyl)methyl-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 4 was carried out using 7-chloro-1,3-dihydro-3(R)-(3'-indolyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one etherate (0.1 g, 0.22 mmole) in place of 1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one, 50% sodium hydride in mineral oil (0.014 g, 0.29 mmole), and methyl iodide (0.045 g, 0.32 mmole) in DMF (2 ml). Chromatography on a six inch (15 cm), 15 mm diameter silica gel column provide the title compound which, after evaporation and in vacuo, was dissolved in acetone, precipitated with water and

filtered. The resulting solid was dried in vacuo at 70°: (mp 134-152 (indistinct)).

The compound showed a single spot by TLC (R_f=0.22, silica gel plate eluted with 5% (v/v) ether/methylene chloride. The NMR spectrum was consistent with the title structure. The compound was 98.9% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 413.

Analysis Calc'd for: $C_{25}H_{20}ClN_3O$:
C, 72.54; H, 4.87; N, 10.15; Cl, 8.57;
Found: C, 72.38; H, 4.88, N, 10.20; Cl, 8.32.

EXAMPLE 32

1,3-Dihydro-5-(2-fluorophenyl)-3(S)-(3'-indolyl) methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 1 was carried out using 0.7 g (3.25 mmole) of 2-amino-2'-fluorobenzophenone, 0.99 g, (3.25 mmole) of Boc-L-tryptophan, and 3.25 ml (3.25 mmole) of 1M DCC/CH_2Cl_2 in 5 ml of THF. The product obtained by silica gel chromatography (10 inch (25 cm) column, 25 mm diameter, methylene chloride and 2% and 3% (v/v) ether/methylene chloride elution) was deprotected and cyclized according to the procedure of Example 2. The cyclization required three days. The resulting mixture was evaporated in vacuo, partitioned between water and methylene chloride, and separated. The aqueous layer was extracted twice with methylene chloride, and the combined methylene chloride layers were washed with water, dried over sodium sulfate, filtered, and evaporated in vacuo. The residue was recrystallized from acetone/ether, and the resulting solid dried in vacuo at 100°: (mp 255-257°).

The compound showed a single component by TLC (R_f=0.59, silica gel plate eluted with 1:1 (v/v) methylene chloride/ether. The NMR spectrum was consistent with the title structure. The mass spectrum showed a molecular ion at m/e = 383. The compound was 99.3% pure by HPLC.

Analysis Calc'd for $C_{24}H_{18}FN_3O$:
C, 75.18; H, 4.73; N, 10.96;
Found: C, 75.45; H, 4.71; N, 11.11.

EXAMPLE 33

1-Benzyl-7-chloro-1,3-dihydro-3(S)-(3'-indolyl) methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 4 was carried out using 7-chloro-1,3-dihydro-3(S)-(3'-indolyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one etherate (0.1 g, 0.22 mmole) in place of 1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one, 50% sodium hydride in mineral oil (0.014 g, 0.29 mmole), and benzyl bromide (0.058 g, 0.34 mmole) in place of methyl iodide. The reaction was run in 1.5 ml of dry DMF. Silica gel chromatography (8 inch (20 cm) column, 15 mm diameter, methylene chloride and 5% (v/v) ether/methylene chloride elution)) and evaporation of the product fractions in vacuo gave the title compound which was dried in vacuo at 60°: (mp 80-120° (indistinct)).

The compound showed a single component by TLC (R_f=0.40, silica gel plate eluted with 5% (v/v) ether/methylene chloride). The NMR spectrum was consistent with the title structure and showed 1/2 mole of cyclohexane. The compound was 99.3% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 489.

Analysis Calc'd for $C_{31}H_{24}ClN_3O \cdot 1/2\ C_6H_{12}$:
C, 76.74; H, 5.68; N, 7.90; Cl, 6.66;
Found: C, 76.56; H, 5.67; N, 7.86; Cl, 7.00.

EXAMPLE 34

7-Chloro-1,3-dihydro-3(R)-(3'-indolyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-thione

7-Chloro-1,3-dihydro-3(R)-(3'-indolyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one etherate (1.0 g, 2.1 mmole) and P_2S_5 (0.51 g, 2.3 mmole) were combined in dry pyridine (16 ml) and heated at reflux for 40 minutes. Pyridine was removed by evaporation in vacuo and the residue treated with ice water and extracted with methylene chloride. The methylene chloride layers were combined, dried over potassium carbonate, filtered, and evaporated in vacuo to give a foam. This material was chromatographed on silica gel (9 inch (23 cm) column, 25 mm diameter, 15% (v/v) ether/methylene chloride elution), and the product fractions evaporated. The residue was recrystallized from acetone/ethyl acetate and the solid dried in vacuo at 90°: (mp 279-280°).

The compound showed a single spot by thin layer chromatography (R_f=0.32, silica gel plate eluted with 10% (v/v) ether/methylene chloride). The NMR spectrum was consistent with the title structure. The compound was 98.6% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 415.
Analysis Calc'd for $C_{24}H_{18}ClN_3S$:
C, 69.30; H, 4.36; N, 10.10; S, 7.71;
Found: C, 69.39; H, 4.39; N, 10.14; S, 7.46.

EXAMPLE-35

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl) methyl-2H-1,4-benzodiazepin-2-[N'-(3-thienoyl)] hydrazide

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-thione (0.28 g, 0.7 mmole) and 3-thienoyl chloride (0.1 g, 0.7 mmole) were combined in ether (5 ml) and THF (1 ml) and stirred at room temperature. After one hour the mixture was filtered and evaporated in vacuo, and the residue chromatographed on silica gel (8 inch (20 cm) column, 25 mm diameter, 1-1/2% followed by 3% (v/v) methanol/methylene chloride elution). The product fractions were evaporated in vacuo and the resulting solid dried in vacuo at 70°: (mp 207-209°( )).

The compound showed a single spot by TLC (R_f=0.4, silica gel plate eluted with 5% (v/v) methanol/methylene chloride). The NMR spectrum was consistent with the title structure. The compound was 92% pure by HPLC.

Analysis Calc'd for $C_{29}H_{22}FN_5OS \cdot 0.2H_2O$:
C, 68.13; H, 4.42; N, 13.70;
Found: C, 68.19; H, 4.30; N, 13.91.

EXAMPLE 36

1,3-Dihydro-1-ethyl-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 4 was carried out using ethyl iodide (0.35 g, 2.25 mmole) in place of methyl iodide. Silica gel chromatography followed by evaporation in vacuo gave the product which was dried at room temperature in vacuo (mp 95-113°).

The compound showed a single spot by thin layer chromatography (R_f=0.44, silica gel plate eluted with 10% (v/v) ether/methylene chloride). The NMR spectrum was consistent with the title structure and showed the presence of approximately 0.15 mole of methylene chloride. The compound was 95.3% pure by HPLC. The mass spectrum showed a molecular ion at me =411.

Analysis Calc'd for: $C_{26}H_{22}FN_3O \cdot 0.15CH_2Cl_2$:
C, 74.04; H, 5.30; N, 9.91;
Found: C, 74.17; H, 5.22; N, 10.02.

EXAMPLE 37

1-Cyclopropylmethyl-1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 4 was carried out using cyclopropylmethylbromide (0.30 g, 2.25 mmole) in place of methyl iodide. The product obtained by chromatography and evaporation was recrystallized from a mixture of methylene, chloride, ether, and hexane, and the resulting solid dried in vacuo at 80°: (mp 207.5 - 208.5°).

The compound showed a single component by TLC (R_f = 0.26, silica gel plate eluted with 4% (v/v) ether/methylene chloride). The NMR spectrum was consistent with the title structure. The compound was 99.6% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 437.

Analysis Calc'd for $C_{28}H_{24}FN_3O \cdot 0.07CH_2Cl_2$:
C, 76.02; H, 5.49; N, 9.48;
Found: C, 75.96; H, 5.42; N, 9.30.

EXAMPLE 38

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl) methyl-1-pentyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 4 was carried out using 1-bromopentane (0.34 g, 2.25 mmole) in place of methyl iodide. The product obtained after silica gel chromatography and evaporation was crystallized from ether and dried in vacuo at 80°: (mp 150-151°).

The compound showed a single component by thin layer chromatography (R_f = 0.37, silica gel plate eluted with 4% (v/v) ether/methylene chloride). The NMR spectrum was consistent with the title structure. The compound was 99.9% pure by HPLC. The mass spectrum showed a molecular ion at me =453.

Analysis Calc'd for: $C_{29}H_{28}FN_3O$:
C, 76.79; H, 6.22; N, 9.26;
Found: C, 76.64; H, 6.39; N, 8.83.

EXAMPLE 39

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl) methyl-1-(3-methylbutyl)-2H-1,4-benzodiazepine-2-one

The procedure of Example 4 was carried out using 1-bromo-3-methylbutane (0.34 g, 2.25 mmole) in place of methyl iodide. The product obtained after silica gel chromatography and evaporation was crystallized from ether and dried in vacuo at 80°: (mp = 198-199.5°).

The compound showed a single component by thin layer chromatography (R_f = 0.30, silica gel plate eluted with 4% (v/v) ether/methylene chloride). The NMR spectrum was consistent with the title structure and showed the presence of 0.2 mole

of ether. The compound was 99.9% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 453.

Analysis Calc'd for: $C_{29}H_{28}FN_3O \cdot 0.2C_4H_{10}O$:
C, 76.42; H, 6.46; N, 8.97;
Found: C, 76.52; H, 6.38; N, 9.01.

EXAMPLE 40

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-1-(2,2,2-trifluoroethyl)-2H-1,4-benzodiazepin-2-one

The procedure of Example 4 was carried out using 2,2,2-trifluoroethyl iodide (0.47 g, 2.25 mmole) in place of methyl iodide. Following addition of the trifluoroethyl iodide, the reaction was heated for 18 hours in an oil bath thermostatted at 65°. Workup and chromatography as described in Example 4 gave a product which was recrystallized from ether and dried in vacuo at 80°: (mp 189-192°).

The compound showed a single component by thin layer chromatography (R_f = 0.50, silica gel plate eluted with 5% (v/v) ether/methylene chloride). The NMR spectrum was consistent with the title structure. The compound was 99.2% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 465.

Analysis Calc'd for: $C_{26}H_{19}F_4N_3O$:
C, 67.09; H, 4.11; N, 9.03;
Found: C, 67.32; H, 4.31; N, 8.98.

EXAMPLE 41

1,3-Dihydro-1-(2-dimethylaminoethyl)-5-(2-fluorophenyl)3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 4 was carried out using 1-chloro-2-(dimethylamino)propane (0.24 g, 2.25

mmole) in place of methyl iodide. Following addition of the chloride, the reaction was stirred at room temperature for 5 days and then worked up as described in Example 4. The chromatographed product was crystallized from methylene chloride/hexane and the resulting solid dried in vacuo at 80°: (mp 200-201°).

The compound showed a single component by TLC (R_f = 0.30, silica gel plate eluted with 5% (v/v) methanol/methylene chloride). The NMR spectrum was consistent with the title structure. The compound was 99.6% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 454.

Analysis Calc'd for: $C_{28}H_{27}FN_4O$:
C, 73.98; H, 5.99; N, 12.33;
Found: C, 73.92; H, 6.00; N, 11.28.

EXAMPLE 42

1,3-Dihydro-1-(ethoxycarbonylmethyl)-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 4 was carried out using ethyl bromoacetate (0.38 g, 2.25 mmole) in place of methyl iodide. The chromatographed product was evaporated and dried in vacuo at room temperature: (mp 88-100°).

The compound showed a single component by TLC (R_f = 0.42, silica gel plate eluted with 10% (v/v) ether/methylene chloride). The NMR spectrum was consistent with the title structure and showed the presence of 0.24 mole of methylene chloride. The compound was 92.6% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 469.

Analysis Calc'd for $C_{28}H_{24}FN_3O_3 \cdot 0.24CH_2Cl_2$:
C, 69.23; H, 5.04; N, 8.58;
Found: C, 69.14; H, 5.09; N, 8.87.

EXAMPLE 43

1-Carboxymethyl-1,3-dihydro-5-(2-fluorophenyl)-3(R)-3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-1-(ethoxycarbonylmethylene)-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one (83.2 mg, 0.177 mmole), and 1 molar sodium hydroxide (0.18 ml, 0.18 mmole) were combined in 1 ml of methanol and stirred at room temperature for 24 hours. The solution was acidified with 1 molar hydrochloric acid, and the mixture evaporated in vacuo. The residue was taken up in methylene chloride, washed with water, dried over sodium sulfate, filtered, and evaporated in vacuo to dryness. The residue was triturated with ether followed by petroleum ether, and filtered to give the product which was dried in vacuo at 80°; (mp 175-180° ( )).

The compound showed a single component by TLC (R_f = 0.52, silica gel plate eluted with 90:10:1:1 (v/v/v/v) methylene chloride/methanol/acetic acid/water). The NMR spectrum was consistent with the title structure and showed the presence of both ether and hexane. The compound was 97.2% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 441.

Analysis Calc'd for $C_{26}H_{20}FN_3O_3 \cdot 0.1C_4H_{10}O \cdot 0.04C_6H_{14} \cdot H_2O$:
C, 68.02; H, 5.05; N, 8.94;
Found: C, 67.91; H, 5.04; N, 8.92.

EXAMPLE 44

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-[3'-(1'-methylindolyl)methyl]-1-methyl-2H-1,4-benzodiazepin-2-one

The method of Example 4 was employed except that the starting material was 1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-1-methyl-2H-1,4-benzodiazepin-2-one (1.3 g, 3.3 mmole). Fifty percent sodium hydride in mineral oil (0.16 g, 3.3 mmole) and methyl iodide (0.47 g, 3.3 mmole) were employed in 10 ml of dry DMF. Following workup and chromatography as in Example 4, the product was obtained having physical properties identical to those reported in Example 4.

EXAMPLE 45

1,3-Dihydro-5-(2-fluorophenyl)-3(R)-[3'-(1'-p-chlorobenzyloylindolyl)methyl]-1-methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 4 was carried out using 1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-1-methyl-2H-1,4-benzodiazepin-2-one (0.345 g, 0.87 mmole) in place of 1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one, and p-chlorobenzoyl chloride (0.26 g, 1.5 mmole) in place of methyl iodide. The reaction, employing 0.047 g (0.97 mmole) of 50% sodium hydride in mineral oil, was carried out in 10 ml of dry DMF. Silica gel chromatography as described in Example 4, followed by evaporation in vacuo and trituration with hexane, gave a solid which was dried in vacuo at 50°: (mp 75° ( )).

The compound showed a single component by TLC (R_f = 0.57, silica gel plate eluted with 4%

(v/v) ether/methylene chloride). The NMR spectrum was consistent with the title structure and verified the presence of approximately 0.3 mole of hexane. The compound was 99.3% pure by HPLC.

Analysis Calc'd for $C_{32}H_{23}FClN_3O.0.3C_6H_{14}$:
C, 72.25; H, 4.88; N, 7.48; Cl, 6.31;
Found: C, 72.42; H, 5.02; N, 7.50; Cl, 6.55.

EXAMPLE 46

7-Chloro-1,3-dihydro-3(R)-[3'(1'-benzylindolyl)methyl] 1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 45 was carried out using 0.042 g (0.88 mmole) of 50% sodium hydride, and benzylbromide (0.16 g, 0.92 mmole) in place of p-chlorobenzoyl chloride. Reaction was conducted in 4 ml of dry DMF. Following silica gel chromatography and evaporation, the product was recrystallized from cyclohexane and dried in vacuo at 60°: (mp 77-80° (indistinct)).

The compound showed a single component by TLC (R_f = 0.59, silica gel plate eluted with 5% (v/v) ether/methylene chloride). The NMR spectrum was consistent with the title structure and showed the presence of 1/3 mole of cyclohexane. The compound was 98.7% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 503.

Analysis Calc'd for $C_{32}H_{26}ClN_3O\cdot 1/3C_6H_{12}$:
C, 76.75; H, 5.68; N, 7.90; Cl, 6.66;
Found: C, 76.50; H, 5.74; N, 7.59; Cl, 6.90.

EXAMPLE 47

1,3-Dihydro-3(RS)-[1-hydroxy-1-(3'-indolyl)]methyl-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

The lithium salt of 1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (1.25 g, 5 mmole) was made according to the procedure of J. Org. Chem. 46, 3945 (1981) using 1.01 g (10 mmole) of diisopropylamine, and 6.7 ml of a 1.5 molar solution (10 mmole) of n-butylithium in hexane. This anion solution was added by syringe to a solution of 0.725 g (5 mmole) of indole-3-carboxaldehyde in 15 ml of dry THF stirred under nitrogen in a dry ice-acetone bath. The mixture was warmed to room temperature, stirred for 1 1/2 hours and then quenched by the addition of saturated sodium chloride solution. The mixture was separated and the aqueous layer extracted twice with methylene chloride (2 x 10 ml). The organic layers were dried over sodium sulfate, filtered and evaporated to dryness in vacuo. The residue was chromatographed on silica gel (230-400 mesh, 8 inch (20 cm) column, 25 mm diameter, 1:1 ether/methylene chloride elution). The evaporated product fractions were crystallized from ether and dried in vacuo at 70°: (mp 218-221°).

The compound showed a single component by TLC (R_f = 0.30, silica gel plate eluted with 1:1 (v/v) ether/methylene chloride). The NMR spectrum was consistent with the title structure. The compound was 90% pure by HPLC. The mass spectrum showed a molecular ion at me = 395.

Analysis Calc'd for $C_{25}H_{21}N_3O_2 \cdot 0.25H_2O$:
C, 75.07; H, 5.42; N, 10.51;
Found: C, 75.04; H, 5.50; N, 10.59.

EXAMPLE 48

1,3-Dihydro-1-methyl-5-phenyl-3-(RS)-(3-thienoyl)-2H-1,4-benzodiazepin-2-one

The procedure of Example 47 was carried out using thiophene-3-carbonyl chloride (730 mg, 5.0 mmol) in place of indole-3-carboxaldehyde. Following chromatography (silica gel, 5% (v/v) Et_2O in CH_2Cl_2), the product was evaporated to dryness and crystallized from Et_2O. The solid was dried *in vacuo* at 65°C: (m.p. 205-8°C).

The compound showed a single spot by TLC (R_f=0.54, silica gel plate, 10% (v/v) Et_2O in CH_2Cl_2). The NMR spectrum was consistent with the title structure. The compound was greater than 92.4% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 360.

Anal. Calc'd for $C_{21}H_{16}N_2O_2S$:
C, 69.98; H, 4.47; N, 7.77.
Found: C, 70.27; H, 4.64; N, 7.69.

EXAMPLE 49

1,3-Dihydro-3-(RS)-[1-hydroxy-1-(3-thienyl)]methyl-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 47 was carried out using thiophene-3-carboxaldehyde (560 mg, 5.0 mmol) in place of indole-3-carboxaldehyde. Following chromatography (silica gel, 15% (v/v) Et_2O in CH_2Cl_2), the product was evaporated to dryness and crystallized from Et_2O. The solid was dried *in vacuo* at 65°C: (m.p. 189-91°C).

The compound showed a single spot by TLC (R_f=0.36, silica gel plate, 15% (v/v) Et_2O in CH_2Cl_2). The NMR spectrum was consistent with

the title structure. The compound was greater than 99.0% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 362.

Anal. Calc'd for $C_{21}H_{18}N_2O_2S$:

C, 69.59; H, 5.01; N, 7.73.

Found: C, 69.62; H, 5.01; N, 7.57.

EXAMPLE 50

1,3-Dihydro-3(RS)-[1-hydroxy-1-[3-(1-methylindolyl)]]-methyl-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (two stereoisomers, A and B)

The procedure of Example 47 was carried out using 1-methylindole-3-carboxaldehyde (797 mg, 5.0 mmol) in place of indole-3-carboxaldehyde. The product diastereomers were separated by chromatography (silica gel, 10% (v/v) Et_2O in CH_2Cl_2) and evaporated to dryness.

A: The faster running component (TLC-R_f=0.41, silica gel plate, 60% (v/v) EtOAc in hexane) was crystallized from Et_2O. The solid was dried *in vacuo* at 65°C: (m.p. 218-21°C).

The compound showed a single spot by TLC. The NMR spectrum was consistent with the title structure. The compound was greater than 96.7% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 409.

Anal. Calc'd for $C_{26}H_{23}N_3O_2$:

C, 76.26; H, 5.66; N, 10.26.

Found: C, 76.26; H, 5.84; H, 10.34.

B: The slower running component (TLC-R_f=0.30, silica gel plate, 60% (v/v) EtOAc in hexane) was

crystallized from Et_2O. The solid was dried in vacuo at 65°C: (m.p. 125-30°C).

The compound was a single spot by TLC. The NMR spectrum was consistent with the title structure and cnfirmed the presence of Et_2O. The compound was greater than 95.7% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 409).

Anal. Calc'd for $C_{26}H_{23}N_3O_2 \cdot 0.9C_4H_{10}O$:
C, 74.66; H, 6.77; N, 8.83.
Found: C, 74.61; H, 6.80; N, 9.10.

EXAMPLE 51

1,3-Dihydro-3(RS)-(1-hydroxy-1-phenyl)methyl-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 47 was carried out using benzyldehyde (0.53 g, 5 mmole) in place of indole-3-carboxaldehyde. The chromatographed product was crystallized from ether and dried in vacuo at 70°: (mp 192-193°).

The compound showed a single component by TLC (R_f = 0.53, silica gel plate eluted with 1:1 (v/v) ether/methylene chloride). The NMR spectrum was consistent with the title structure and showed the presence of 0.1 mole of ether. The compound was 99.9% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 338.

Analysis Calc'd for $C_{23}H_{20}N_2O_2 \cdot 0.1C_4H_{10}O$:
C, 77.24; H, 5.82; N, 7.70:
Found: C, 77.11; H, 5.83; N, 7.93.

EXAMPLE 52

1,3-Dihydro-3(RS)-[1-hydroxy-1-(2-thienyl)]methyl-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 47 was carried out using 2-thiophene-carboxaldehyde (0.56 g, 5 mmole) in place of indole-3-carboxaldehyde. The chromatographed and evaporated product was crystallized from ether and dried in vacuo at 70°: (mp 184-185°).

The compound showed a single component by TLC (R_f = 0.54, silica gel plate eluted with 1:1 (v/v) ether/methylene chloride). The NMR spectrum was consistent with the title structure. The compound was 99.8% pure by HPLC.

Analysis Calc'd for $C_{21}H_{18}N_2O_2S$:
C, 69.59; H, 5.01; N, 7.73;
Found: C, 69.59; H, 5.10; N, 8.06.

EXAMPLE 53

1,3-Dihydro-3-(RS)-hydroxy-1-methyl-5-phenyl-3-(3'-thienoyl)-2H-1,4-benzodiazepin-2-one (A) and 1,5-Dihydro-5-(RS)-hydroxy-1-methyl-5-phenyl-3-(3'-thienoyl)-2H-1,4-benzodiazepin-2-one (B)

The procedure of Example 47 was carried out using 0.75 g (5 mmole) of 3-thienoyl chloride in place of indole-3-carboxaldehyde. In this reaction, the THF employed was subsequently shown to contain significant quantities of organic peroxides. Workup and chromatography as in Example 47 provided two products each of which was evaporated in vacuo and crystallized from ether.

A: The first product obtained was A, which was dried in vacuo at 70°: (mp 193-194°).

The compound showed a single component by TLC (R_f = 0.57, silica gel plate eluted with 1:1 (v/v) methylene/chloride ether). The NMR spectrum was consistent with the title structure. The compound was 99.4% pure by HPLC. The mass spectrum showed a molecular ion at m/e = 376. The infrared spectrum showed a strong absorption at 1675 cm^{-1}.

Analysis Calc'd for $C_{21}H_{16}N_2O_3S$:
C, 67.00; H, 4.28; N, 7.44;
Found: C, 67.04; H, 4.37; N, 7.49.

B: The second compound obtained was B, which was dried in vacuo at 70°: (mp 173-175°).

The compound showed a single component by TLC (R_f = 0.64, silica gel plate eluted with 1:1 methylene chloride/ether). The NMR spectrum was consistent with the title structure. The mass spectrum showed a molecular ion at m/e = 376. The compound was 99.6% pure by HPLC. The infrared spectrum showed strong absorption at 1695 and 1720 cm^{-1}.

Analysis Calc'd for $C_{21}H_{16}N_2O_3S$:
C, 67.00; H, 4.28; N, 7.44;
Found: C, 66.91; H, 4.46; N, 7.32.

EXAMPLE 54

7-Chloro-1,3-dihydro-3(R)-[(2',3'-dihydro-2'-oxo-1'H-indol-3'-yl)methyl]-5-phenyl-2H-1,4-benzodiazepin-2-one

7-Chloro-1,3-dihydro-3(R)-indolylmethyl-5-phenyl-2H-1,4-benzodiazepin-2-one (200 mg, 0.5 mmol) was dissolved in DMSO (4.8 g, 10 mmol) followed by the addition of concentrated HCl (5 mmol). The molar

ratio of DMSO to HCl was 2:1. Additional reagents were added to drive the reaction to completion. The additions were: 0.71 ml DMSO 1.54 ml DMSO
0.4 ml HCl 0.75 ml HCl

When little starting material remained, the reaction was poured into an Erlenmeyer flask with water (20 ml), and 5 g of $NaHCO_3$ was added. Water (100 ml) was added and the mixture was extracted with 4x50 ml of n-butanol. The n-butanol solution was washed with water (3x100 ml). The n-butanol solution was evaporated and the residue was dissolved in ether and purified by preparative TLC.

The product was a pair of diasteriomers; the NMR spectrum was consistent with the title compound.

HPLC indicated two components: 54% and 43%.

TLC in 95/5/0.5 $CHCl_3$-MeOH-H_2O R_f=0.3 (silica gel GF)

Mass Spec. gave a (M+1) at 416.

EXAMPLE 55

7-Chloro-1,3-dihydro-3(R)-[(3'-(2,4-dinitrophenyl)-imidazol-5'-yl)-methyl]-5-phenyl-2H-1,4-benzodiazepin-2-one

Boc-DNP-D-Histidine (1.7 g, 4 mmol) and 2-amino-5-chlorobenzophenone (0.9 g, 4 mmol) were combined in 10 ml of THF and stirred until a clear orange solution was obtained. 4.3 mL of DCC (1M) in THF was added and the reaction was stirred overnight. The reaction was filtered and evaporated. The residue was purified by flash chromatography on a silica gel 60 column with a 90:10 chloroform ether solvent system.

The resultant t-BOC protected compound was dissolved in 30 ml of ethyl acetate. The solution was cooled to -25°C. HCl gas was added until the solution was saturated. The temperature was allowed to rise to 0°C. When the reaction was complete by TLC, the ethyl acetate was evaporated and the residue was dissolved in methanol. The pH of the solution was adjusted with 10% aqueous sodium hydroxide to pH 9. After the reaction stirred overnight, the solvent was evaporated and the residue was chromatographed on a silica gel 60 column with chloroform, to give the title compound.

HPLC: 91%.

TLC: R_f=0.6 in 90/10/1 $CHCl_3$-MeOH-aqueous ammonia (silica gel GF)

Mass Spec. molecular ion at 516.

NMR agreed with the title compound.

Elemental analysis for $C_{25}H_{17}ClN_6O_5 \cdot 1.8H_2O$

Calcd: C, 54.65; H, 3.82; N, 15.30.

Observed: C, 54.38; H, 3.89; N, 15.31.

EXAMPLE 56

7-Chloro-1,3-dihydro-3(R)-(3'-imidazol-5'-yl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

This compound was obtained as a second product from the reaction sequence of Example 55. This material, which had a positive Sanger test for histidine, eluted from the silica column after the compound of Example 55, HPLC: 87%.

TLC: R_f-0.3 in 90/10/1 $CHCl_3$-MeOH-aqueous ammonia (silica gel GF).

Mass Spec. molecular ion at 350.

NMR was consistent with the title compound.

Elemental Analysis for: $C_{19}H_{15}ClN_4O$ 0.93 H_2O 0.28NH_3
Calcd: C, 61.29; H, 4.79; N, 16.33.
Found: C, 61.68; H, 5.12; N, 16.61.

EXAMPLE 57

3(RS)-[3'-(5'-Bromoindolyl)methyl]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

The synthesis was carried out as described for Example 55 starting with Boc-5-bromo-DL-tryptophan and 2-aminobenzophenone. The crude product was purified by column chromatography (silica gel) using 90/10 chloroform-ether as the elution solvent.

HPLC: 99%.

Elemental analysis calcd:
N, 8.91; C, 61.15; H, 4.41
Found: N, 8.43; C, 61.43; H, 4.20.
Mass Spec. molecular ion at 443.
NMR: The NMR was in agreement with the title compound.

EXAMPLE 58

5-o-Carboxyphenyl-1,3-dihydro-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one

2-Amino-2'-carboxybenzophenone (2.41 g, 10 mmol) was suspended in THF, CH_2Cl_2, EtOAc and tryptophanyl chloride hydrochloride (2.59 g, 10 mmol) was added. The mixture was stirred at room temperature until reaction was complete by TLC. A solid was collected by filtration, dried, and dissolved in 40 ml of methanol. The pH of the solution was adjusted to a pH of 8-10 with 10% aqueous sodium hyroxide. After standing at room temperature for about 3 days, the solution was

acidified to a pH of about 3. The solvent was evaporated and the residue was dissolved in 95/5 $CHCl_3/CH_3OH$ and flash chromatographed on a silica gel 60 column with a 95:5 and 90:10 chloroform-methanol solvent system to give the title compound.

HPLC: 96%.

Elemental analysis calcd:

C, 61.73; H, 3.97; N, 8.38

Found: C, 61.70; H, 4.09; N, 8.48.

Mass Spec. molecular ion observed at 409.

NMR: The spectrum agreed with the title compound.

EXAMPLE 59

1,3-Dihydro-3(RS)-[3'-(5'-fluoroindolyl)methyl]-5-o-fluorophenyl-2H-1,4-benzodiazepin-2-one

5-Fluorotryptophyl chloride hydrochloride (1.38 g, 5 mmole), prepared from 5-fluoro-DL-tryptophan and PCl_5 in acetylchloride, was suspended in 15 ml of THF. 2-Amino-2'-fluorobenzophenone 1.07 g (5.0 mmol) was added to the stirred mixture. After stirring overnight the solvent was evaporated and the solid was dissolved in 50 ml of methanol. The pH of the solution was adjusted to 8-9 with 10% aqueous sodium hydroxide. The solution stood for 24 hours at room temperature. The solvent was evaporated and the crude reaction product was purified by flash chromatography with 98:2 chloroform/methanol to give the title compound.

TLC: R_f=0.3 in 97:3 $CHCl_3/CH_3OH$ (silica gel GF).

Elemental analysis calcd for $C_{24}H_{17}F_2N_3O$ .0.18$CHCl_3$

C, 68.75; H, 4.10; N, 9.94

Found: C, 68.78; H, 4.04; N, 9.85.
NMR was in agreement with the title compound.

EXAMPLE 60

1,3-Dihydro-3(RS)-[3'-(6'-fluoroindolyl)methyl]-5-o-fluorophenyl-2H-1,4-benzodiazepin-2-one

The compound was prepared according to the procedure of Example 59, using 6-fluorotryptophyl chloride hydrochloride in place of the 5-fluoro compound.

The final product was obtained as a solid which crystallized in pure form from chloroform.

TLC: R_f=0.4 in 97:3 $CHCl_3/CH_3OH$ (silica gel GF)

Elemental analysis calcd:
C, 70.62; H, 4.20; N, 10.26
Found: C, 70.62; H, 4.10; N, 10.25.
NMR was in agreement with the title compound.

EXAMPLE 61

2-N-[2(RS)3-bis-(Boc-amino)propanoyl]amino-2'-fluorobenzophenone

The procedure of Example 1 was carried out using 2-amino-2'-fluorobenzophenone (430 mg, 2.0 mmole), 2(R,S),3-bis-(Boc-amino)propionic acid (617 mg, 2.03 mmole), and dicyclohexylcarbodiimide (2.03 ml of a 1.0 M solution in methylene chloride) in 10 ml of methylene chloride. Filtration, concentration in vacuo and flash chromatography (silica gel, 10% ethyl ether in methylene chloride) gave a foam, the PMR spectrum of which was consistent with the title compound.

EXAMPLE 62

2-N-[2(RS),3-diphthalylaminopropanoyl]amino-2'-fluoro-benzophenone

2-Amino-2'-fluorobenzophenone (2.10 g, 9.8 mmole) was reacted with 2,3-diphthalylaminopropionyl chloride (5 g, 9.8 mmole) in 100 ml of tetrahydrofuran. After 2.5 hours the reaction mixture was rotoevaporaed to give 7 g of a yellow foam. The foam was heated for 30 minutes in 6N hydrochloric acid (100ml) and the resulting off-white solid collected and dried. Recrystallization from ethyl acetate afforded the analytical sample, m.p. 210.5-211.5°.

NMR (CD_3OD): in agreement with title compound.

Analysis Calc'd for $C_{32}H_{20}FN_3O_6$

N, 7.48; C, 68.45; H, 3.59.

Found: N, 7.46; C, 68.59; H, 3.63.

EXAMPLE 63

1,3-Dihydro-5-(2'-fluorophenyl)-3(RS)-aminomethyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 2 was carried out in which 2-N-[2(RS)-((1,1-dimethylethoxy)carbonyl)-amino-3-((1,1-dimethylethoxy)carbonyl)aminopropanoyl]-amino-2'-fluorobenzophenone (600 mg, 1.2 mmole) was reacted in succession with excess HCl gas in ethyl acetate (15 ml) at 0° and then sodium hydroxide (0.1M solution) in aqueous methanol (10 ml). The pH of the reaction mixture was approximately 9.0. Work-up afforded the title compound as a solid, mp 168-169°; in 90% yield.

NMR ($CDCl_3$): Spectrum in agreement with title compound.

MS (14 ev.): 283 (M^+) 253.

Analysis Calc'd for $C_{16}H_{14}FN_3O \cdot 0.05C_6H_{14}$
N, 14.61; C, 68.07; H, 5.15.
Found: N, 14.87; C, 68.21; H, 5.33.

EXAMPLE 64

1,3-Dihydro-5-(2'-fluorophenyl)-3(RS)-aminomethyl-2H-1,4-benzodiazepin-2-one

2-N-[2(RS),3-diphthalylaminopropanoyl]amino-2'-fluorobenzophenone (1.07 g, 1.90 mmole) was suspended in 55 ml of methanol and treated with 1 ml of 95% hydrazine. The reaction mixture was protected from moisture and stirred at room temperature. Within one hour, the reaction mixture became homogeneous. On further reaction, phthalhydrazide precipitated from solution. After 14 hours, the reaction was filtered and the filtrate concentrated. The residue was partitioned between methylene chloride and water; the organic phase was washed wth water until it was free of hydrazine (Tollen's reagent negative), then dried and concentrated to give 480 mg of an oil which crystallized on standing. Trituration of the resulting solid with ether gave the analytical sample, m.p. 168-169°, identical spectroscopically with the material prepared in Example 63.

EXAMPLE 65

1,3-Dihydro-5-(2'-fluorophenyl)-3(R)-(4-amino)butyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 64 was followed whereby 2-N-[2(R),6-diphthalylaminohexanoyl]amino-2'-fluorobenzophenone (5.4 g) was deprotected and cyclized with 10 ml of 95% hydrazine in 150 ml of

methanol. Workup afforded 1.35 g of product which was purified via silica gel chromatography (chloroform-methanol-ammonia, 80:30:4 v/v).
NMR ($CDCl_3$): in agreement with title compound.
Analysis Calc'd for $C_{19}H_{20}FN_3O \cdot 0.17CHCl_3$
N, 12.15; C, 66.60; H, 5.88.
Found: N, 12.32; C, 66.66; H, 6.05.

EXAMPLE 66

1,3-Dihydro-5-(2'-fluorophenyl)-3(RS)-(benzyloxycarbonyl)aminomethyl-2H-1,4-benzodiazepin-2-one

To a solution of 50 ml of methylene chloride containing 260 mg (0.91 mmol) of 1,3-dihydro-5-(2-fluorophenyl)-3(RS)-aminomethyl-2H-1,4-benzodiazepin-2-one and 224 mg (1.83 mmol) of 4-dimethylaminopyridine was added 0.51 ml (3.57 mmol) of benzylchloroformate. The resulting reaction mixture was allowed to stand at room temperature overnight and then was diluted with methylene chloride (200 ml). The reaction was then washed in succession with saturated sodium bicarbonate solution and brine, then dried ($MgSO_4$) and concentrated. The residual oil was chromatographed on silica gel (chloroform-methanol-ammonia, 95:5:0.5 v/v elution) to afford 370 mg of the analytical product, m.p. 88° (soften), 90-92°C.
TLC: Single component, R_f = 0.35 (95:5:0.5, chloroform - methanol - ammonia).
NMR: Consistent with title structure.
Anal. calc'd for $C_{24}H_{20}FN_3O_3 \cdot 1/4\ H_2O$
N, 9.96; C, 68.32; H, 4.89;
Found: N, 9.86; C, 68.45; H, 5.15.

EXAMPLE 67

1,3-Dihydro-5-(2'-fluorophenyl)-3(RS)-(3-thiophenecarbonyl)aminomethyl-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-5-(2'-fluorophenyl)-3(RS)-aminomethyl-2H-1,4-benzodiazepin-2-one (140 mg, 0.49 mmole) and 3-thiophenecarbonyl chloride (88 mg, 0.60 mmole) were dissolved in 10 ml of dry tetrahydrofuran at room temperature. To this solution was added 69 µl of triethylamine. After addition was complete, stirring was continued for 15 minutes more and the reaction mixture was partitioned between ethylacetate (60 ml) and sodium bicarbonate solution (sat.). The organic phase was washed with 10% sodium hydroxide solution (1 x 20 ml) and then with 10% hydrochloric acid solution. From this acidic solution were deposited off-white crystals, after overnight standing. The solid was washed with water and dried to give 140 mg of the analytical product, mp 237-240° (An additional 70 mg of product was obtained as the free base after concentration of the organic extracts.) The analytical product was greater than 98% pure by HPLC.

MS (14 ev.): 393 (M-HCl), 266.

NMR ($DMSO-d_6$): in agreement with title compound.

Analysis Calc'd for $C_{21}H_{17}ClFN_3O_2S$:
N, 9.77; C, 58.67; H, 3.98.
Found: N, 9.89; C, 58.75; H, 4.17.

EXAMPLE 68

1,3-dihydro-5-(2'-fluorophenyl)-3(RS)-(2-indolecarbonylaminomethyl)-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-5-(2-fluorophenyl)-3(RS)-aminomethyl-2H-1,4-benzodiazepin-2-one (80 mg, 0.282

mmole) and indole-2-carbonyl chloride (53 mg, 0.30 mmol) were mixed in 5 ml of methylene chloride at room temperature. The homogeneous reaction mixture was protected from moisture and treated with 42 µl (0.30 mmole) of triethylamine. Within five min., triethylamine hydrochloride precipitated. The reaction mixture was stirred at room temperatre overnight and then partitioned between methylene chloride and saturated sodium bicarbonate solution. The resulting solid was collected, washed with water and dried over P_2O_5 at 70°C. In this way, 39 mg of the analytical product was obtained, m.p.: 315-317° (d).

NMR(DMSO-d_6): Consistent with the title structure.

MS: Molecular ion at m/e = 426.

Anal. calc'd for $C_{25}H_{19}FN_4O_2$·1.25 H_2O

C, 66.88; H, 4.82; N, 12.48;

Found: C, 66.76; H, 4.52. N, 12.25;

EXAMPLE 69

1,3-Dihydro-3(RS)-[3'-(RS)-(1,3-dihydro-5-(2'-fluorophenyl)-2H-1,4-benzodiazepin-2-one)]methylamino-methyl-5-(2'-fluorophenyl)-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-5-(2'-fluorophenyl)-3(RS)-amino-methyl-2H-1,4-benzodiazepin-2-one (60 mg, 0.21 mmole) was dissolved in 3 ml of isopropanol and treated with triethylamine (30 µl, 0.22 mmole). The resulting solution was heated to reflux for 18 hours, cooled and concentrated. The residual oil was chromatographed on silica gel (chloroform-methanol-ammonia, 90:10:1 v/v) to give 25 mg of the desired product as an off-white solid, mp 155-158° (with gas evolution).

MS (FAB): 550 (M+H), 549 (M^+), 282 (base peak).

NMR ($CDCl_3$): in agreement with title compound.
Analysis Calc'd for $C_{32}H_{25}F_2N_5O_2 \cdot 0.35\ CHCl_3$:
N, 11.84; C, 65.70; H, 4.32.
Found: N, 11.68; C, 65.53; H, 4.46.

EXAMPLE 70

1,3-Dihydro-5-(2'-fluorophenyl)-3-(RS)-(6'-chloropyrazinyl)aminomethyl-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-aminomethyl-2H-1,4-benzodiazepin-2-one (72 mg, 0.25 mmol), 2,6-dichloropyrazine (45 mg, 0.30 mmol) and anhydrous potassium carbonate (83 mg, 0.60 mmol) were combined at room temperature with 2 ml of dry dimethylformamide. The resulting suspension was stirred rapidly for 24 hours and 37 mg more of 2,6-dichlorpyrazine was added. After 72 hours total reaction time, the reaction mixture was poured into water (10 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated to give 70 mg of crude product. The analytical sample was obtained by preparative thick layer chromatography (chloroform - methanol - ammonia, 95:5:0.5 v/v one elution).
R_f = 0.25, m.p. 140° (soften), 148-152°.
NMR ($CDCl_3$): Consistent with the title structure.
MS (14 ev): 395 (M^+), 266, 254, 211.
Anal. calc'd for $C_{20}H_{15}ClFN_5O.1/4\ H_2O$:
N, 17.49; C, 60.00; H, 3.90;
Found: N, 16.59; C, 59.87; H, 3.90.

EXAMPLE 71

2-N-Methyl-N-[2(RS),3-diphthalylaminopropanoyl]amino-2'-fluorobenzophenone

Following the procedure of Example 4, 2-N-[2(RS),3-diphthalylaminopropanoyl]amino-2'-fluorobenzophenone (677 mg, 1.20 mmole) was converted to the title compound with sodium hydride (63 mg, 1.31 mmole) and methyliodide (81.5 µl, 1.31 mmole) in 5 ml of N,N-dimethylformamide. Work-up afforded the crude product which was purified by silica gel chromatography (ethyl acetate-hexane elution, 3:2 v/v); the analytical sample was obtained as white prisms by recrystallizing the chromatographed material from ethyl acetate, mp 252°.

MS (14 ev.): 575 (M^+), 453, 429, 309.

NMR ($CDCl_3$): in agreement with title compound.

Analysis Calc'd for $C_{33}H_{22}FN_3O_6 \cdot 0.15\ C_4H_8O_2$:
N, 7.13; C, 68.54; H, 3.94.

Found: N, 7.12; C, 68.43; H, 4.26.

EXAMPLE 72

1,3-Dihydro-5-(2'-fluorophenyl)-3(RS)-aminomethyl-1-methyl-2H-1,4-benzodiazepin-2-one

Following the procedure of Example 64, 2-N-methyl-N-[2(RS),3-diphthalylaminopropanoyl]amino-2'-fluorobenzophenone (220 mg, 0.38 mmole) was converted to the title compound with 95% hydrazine (1 ml) in 40 ml of methanol. The analytical material was obtained via chromatography on silica gel (chloroform-methanol-ammonia, 90:10:1 v/v). The PMR spectrum ($CDCl_3$) confirmed the structure of the product; N-methyl proton at 3.46 ppm.

EXAMPLE 73

3(RS)-(2-indolecarbonylamino)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

3-(RS)-Amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (75 mg, 0.298 mmol), and indole-2-carbonyl chloride (58.8 mg, 0.327 mmol) were combined in CH_2Cl_2 (2 ml) and the pH adjusted to 9.0 with triethylamine (41 µl, 0.298 mmol). After stirring 10 min., the reaction was chromatographed on silica gel (180/10/1/1 of CH_2Cl_2/MeOH/H_2O/HOAc). The combined product fractions were washed with dilute $NaHCO_3$ (aq) (1X), H_2O (1X) and brine (1X), dried over $MgSO_4$, filtered and stripped to give the title compound as a white solid from ether: (m.p. 265-268°).

TLC: Silica GF (10% MeOH in CH_2Cl_2), R_f = 0.63, single homogeneous component.

NMR: Consistent with title structure and verifies the presence of 0.2 $(C_2H_5)_2O$.

HPLC: Greater than 99.2% pure.

M.S.: Mol. Ion = 394 m/e (free base).

Anal. Calc'd for $C_{24}H_{18}N_4O_2 \cdot 0.2$ $(C_2H_5)_2O$:

C, 72.78; H, 4.93; N, 13.69;

Found: C, 72.45; H, 4.60; N, 13.65.

EXAMPLE 74

1,3-Dihydro-3(RS)-[2-(3-indolyl)ethyl]amino-5-phenyl-2H-1,4-benzodiazepin-2-one

3-(RS)-Chloro-1,3,-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one (68 mg, 0.25 mmol), 3-(2-amiono-ethyl)indole (40 mg, 0.25 mmol) and sodium hydroxide (0.1 ml of 2.5N solution) were combined in methanol

(4 ml) and stirred at room temperature for 18 hours. The mixture was evaporated in vacuo, and the residue was dissolved in methylene chloride and chromatographed on silica gel (5% v/v MeOH in CH_2Cl_2). The product fractions were evaporated in vacuo and the resulting solid crystallized from ether and dried in vacuo at 60°: (m.p. 196-197.5 (d)).
TLC: Single spot (R_f = 0.46, silica gel plate, 10% (v/v) MeOH in CH_2Cl_2).
NMR: The spectrum was consistent with the title structure and verified the presence of CH_2Cl_2.
HPLC: Greater than 94% pure.
MS: A molecular ion at m/e = 394.
Anal. calc'd. for $C_{25}H_{22}N_4O.0.13\ CH_2Cl_2$:
C, 74.43; H, 5.53; N, 13.82;
Found: C, 74.62; H, 5.47; N, 13.62.

EXAMPLE 75

3(RS)-[3-(3-indole)propionylamino]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 77 was carried out using 3-(3-indolyl)propionic acid (0.076 g, 0.4 mmol) in place of BOC-L-tryptophan. The product was chromatographed on silica gel using a gradient of 1:1 Et_2O/CH_2Cl_2 containing 0 to 2% CH_2OH. The product was crystallized from acetone and dried in vacuo at 60°: (m.p. 176-182°).
TLC: Single spot (R_f = 0.66, silica gel plate, 10% (v/v) MeOH in CH_2Cl_2).
NMR: The spectrum was consistent with the title structure.
HPLC: 99.7% pure.
MS: A molecular ion at m/e = 422.

Anal. calc'd for $C_{26}H_{22}N_4O_2 \cdot 0.5\ H_2O$:
C, 72.37; H, 5.37; N, 12.99;
Found: C, 72.31; H, 5.57; N, 12.98.

EXAMPLE 76

3(RS)-(3-indoleacetylamino)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

3-(RS)-Amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (75 mg, 0.298 mmol) and indole-3-acetyl chloride (57.8 mg, 0.298 mmol) were combined in CH_2Cl_2 (2 ml) and the pH adjusted to 9.0 with triethylamine (TEA) 41 ml, 0.298 mmol). After stirring 15 min., a second portion of indole-3-acetyl chloride (44 mg, 0.175 mmol) and TEA (30 µl, 0.215 mmol) were added and the reaction stirred an additional 15 min. The completed reaction was diluted with CH_2Cl_2, washed with H_2O (1X) and brine (1X), dried over $MgSO_4$, filtered and stripped to dryness in vacuo. The residue was chromatographed on silica gel (5% MeOH in CH_2Cl_2) to give the title compound as a pinkish solid from Et_2O: (m.p. 264-265°).
TLC: Silca GF (10% MeOH in CH_2Cl_2), R_f = 0.44, single homogeneous component.
NMR: Consistent with title structure.
HPLC: Greater than 93.1% pure.
M.S.: molecular ion at m/e = 408.
Anal. calc'd for $C_{25}H_{20}N_4O_2$:
C, 73.51; H, 4.94; N, 13.72;
Found: C, 73.54; H, 4.94; N, 13.32.

EXAMPLE 77

3(RS)-(Boc-L-tryptophyl)amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

3-(RS)-Amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (0.1 g, 0.4 mmol), BOC-L-tryptophan (0.12 g, 0.4 mmol), and DCC (0.4 ml of a 1 M solution in CH_2Cl_2, 0.4 mmol) were combined in 2 ml of THF to which were added 2 ml of DMF and 2 ml of CH_2Cl_2. The mixture was treated with triethylamine (0.11 ml), stoppered, and stirred at room temperature for four days. The mixture was treated with citric acid solution (10%, 3 ml) and CH_2Cl_2 (5 ml), shaken and separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 5 ml). The combined organic layers were washed with citric acid (10%, 2 x 5 ml), sodium bicarbonate (10%, 2 x 5 ml), and H_2O (10 ml), dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel (1:1 (v/v) Et_2O/CH_2Cl_2) and the combined product fractions evaporated to dryness in vacuo. The residue was triturated with petroleum ether and the solid dried in vacuo at 70°: (m.p. 173-177° (↑)).

TLC: Single spot (R_f = 0.56, silica gel plate, 10% (v/v) CH_3OH in CH_2Cl_2).

NMR: The spectrum was consistent with the title structure and verified the presence of two diastereomers.

HPLC: Greater than 99.7% pure (36% and 63.7%).

MS (PAB): a molecular ion at m/e = 537.

Anal. calc'd for $C_{31}H_{31}N_5O_4$:

C, 69.25; H, 5.81; N, 13.03;

Found: C, 69.48; H, 6.18; N, 12.96.

EXAMPLE 78

1-Carboxymethyl-1,3-dihydro-3(RS)-(2-indolecarbonylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 4 was carried out using 1,3-dihydro-3(RS)-(2-indolecarbonylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one (0.87 g, 2.2 mmol) in place of 1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one and ethyl bromoacetate (0.38 g, 2.25 mmole) in place of methyl iodide. The chromatographed product (7% ether in CH_2Cl_2) (0.073 g, 0.15 mmol) and sodium hydroxide (0.2 ml, 1N, 0.2 mmol) were stirred together in CH_3OH (1 ml) at room temperature for 18 hours. The mixture was concentrated in vacuo, diluted to 3 ml with H_2O, made acidic with 1N HCl, and extracted with CH_2Cl_2 (3 x 5 ml). The combined organic layers were treated with methanol (1 ml) to dissolve precipitated solid, dried over Na_2SO_4, filtered, and evaporated to dryness in vacuo. The residue was crystallized from ether (4 ml) and the solid dried in vacuo at 80°: (m.p. 275-278° (d) (↑)).

TLC: A single spot (R_f = 0.21, silica gel plate, 180:10:1:1 (v/v/v/v) CH_2Cl_2:MeOH:HOAc: H_2O).

NMR: Spectrum was consistent with the title structure and verified with presence of Et_2O and CH_2Cl_2.

HPLC: Greater than 98.5% pure.

MS: A molecular ion at m/e = 452.

Anal. calc'd for $C_{26}H_{20}N_4O_4 \cdot 0.3$ $CH_2Cl_2 \cdot 0.3$ $C_4H_{10}O$

C, 66.03; H, 4.76; N, 11.20;

Found: C, 65.93; H, 4.56; N, 11.22.

EXAMPLE 79

1,3-Dihydro-3(RS)-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (A) and 1,3-dihydro-1-methyl-3(RS)-[2-(1-methylindole)carbonylamino]-5-phenyl-2H-1,4-benzodiazepin-2-one (B)

The procedure of Example 4 was carried out using 1,3-dihydro-3(RS)-(2-indolecarbonylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one (0.87 g, 2.2 mmol) in place of 1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one. Chromatography using 7% (v/v) diethyl ether in CH_2Cl_2 and evaporation of the product fractions in vacuo gave A and B which were each crystallized from ether and dried in vacuo at 80°.

Compound A: (m.p. 268-270° (d))

TLC: A single spot (R_f = 0.43, silica gel plate, 10% (v/v) Et_2O in CH_2Cl_2).

NMR: Spectrum was consistent with the title structure and verified the presence of Et_2O and CH_2Cl_2.

HPLC: 99% pure.

MS: A molecular ion at m/e = 408.

Anal. calc'd for $C_{25}H_{20}N_4O_2 \cdot 0.15 CH_2Cl_2 \cdot 0.1 C_4H_{10}O$:

C, 71.60; H, 5.01; N, 13.07;

Found: C, 71.79; H, 5.01; N, 13.01.

Compound B: (m.p. 202.5°-203°).

TLC: A single spot (R_f = 0.67, silica gel plate, 10% (v/v) Et_2O in CH_2Cl_2).

NMR: Spectrum was consistent with the title structure.

HPLC: Greater than 98.2% pure.

MS: A molecular ion at m/e = 422.

Anal. calc'd for $C_{26}H_{22}N_4O_2$:

C, 73.91; H, 5.25; N, 13.26;

Found: C, 74.05; H, 5.20; N, 13.51.

EXAMPLE 80

1,3-Dihydro-1-methyl-3(RS)-(4-chlorophenylcarbonyl)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

To a suspension of sodium hydride (50%) (84 mg, 1.82 mmole) in 4 ml of dry dimethylformamide at 0°C was added, under nitrogen, 1,3-dihydro-3(RS)-(4-chlorophenylcarbonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (648 mg, 1.59 mmole). The resulting reaction mixture became homogeneous over a one-hour period, was stirred one hour more at 0°C and then treated with iodomethane (108 µl, 1.74 mmole). The reaction mixture was warmed to room temperature and after one hour was quenched with brine. The aqueous mixture was extracted with ethyl acetate and the combined organic extracts were washed with brine. Rotoevaporation of the dried extracts ($MgSO_4$) gave a semi-solid which was chromatographed on silica gel (chloroform-methanol-ammonia 95:5:0.5 v/v elution) to give 130 mg of recovered starting material and 360 mg of the analytical sample R_f = 0.78, m.p. 171.5-172°C.

NMR ($CDCl_3$): consistent with the title structure

MS (14 ev): 421 (M^+) 282, 266, 255,241.

Analysis calc'd for $C_{23}H_{17}ClFN_3O_2$

Calc'd: N, 9.96; C, 65.48; H, 4.06

Found: N, 10.08; C, 65.79; H, 4.08.

EXAMPLE 81

1,3-Dihydro-5-(2-fluorophenyl)-3(RS)-(2-indolecarbonylamino)-1-methyl-2H-1,4-benzodiazepin-2-one (A) and 1,3-Dihydro-5-(2-fluorophenyl)-1-methyl-3(RS)-[2'-(1-methylindole)carbonylamino]-2H-1,4-benzodiazepin-2-one (B)

The procedure of Example 4 was carried out using 1,3-dihydro-5-(2-fluorophenyl)-3(RS)-(2-indolecarbonylamino)-2H-1,4-benzodiazepin-2-one (0.91 g, 2.2 mmole) in place of 1,3-dihydro-5-(2-fluorophenyl)-3(R)(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one. Chromatography using 10% (v/v) diethyl ether in CH_2Cl_2 and evaporation of the product fractions in vacuo gave A and B which were each crystallized from Et_2O/CH_2Cl_2 (2/1, v/v) and dried in vacuo at 40°C.

Compound A: (m.p. 282-283.5°).

TLC: A single spot (R_f = 0.53, silica gel plate, 10% (v/v) Et_2O in CH_2Cl_2).

NMR: The spectrum was consistent with the title structure and verified the presence of ether (1/2 mole) and CH_2Cl_2 (3/4 mole).

HPLC: Greater than 97% pure.

MS: A molecular ion at m/e = 426.

Anal. calc'd for $C_{25}H_{19}FN_4O_2 \cdot 0.5\ C_4H_{10}O \cdot 0.75\ CH_2Cl_2$:
C, 63.22; H, 4.88; N, 10.63;
Found: C, 63.41; H, 4.66; N, 10.59.

Compound B: (m.p. 178-181°)

TLC: A single spot (R_f = 0.76, silica gel plate, 10% (v/v) Et_2O in CH_2Cl_2).

NMR: The spectrum was consistent with the title structure.

HPLC: Greater than 89% pure.
M.S.: A molecular ion at m/e = 440.
Anal. calc'd for $C_{26}H_{21}FN_4O_2.0.75\ H_2O$:
C, 68.78; H, 4.99; N, 12.34;
Found: C, 68.76; H, 4.73; N, 12.38.

EXAMPLE 82

3(RS)-(2(S)-tert-Butoxycarbonylamino-3-phenylpropanoylamino)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

3-(RS)-Amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (1.3 g, 5.17 mmole), Boc-L-phenylalanine (1.37 g, 5.17 mmole), HBT (0.70 g, 5.17 mmole), and EDC (0.99 g, 5.17 mmole) were combined in DMF (30 ml) and stirred at room temperature. The pH of the mixture was adjusted to 9.5 with triethylamine. After 1/2 hour, the DMF was removed *in vacuo* and the residue treated with 10% citric acid (10 ml), neutralized with Na_2CO_3 and extracted with CH_2Cl_2 (3 x 15 ml). The combined organic layers were washed with water, dried over Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel (90/3/0.3/0.3 CH_2Cl_2/MeOH/H_2O/HOAc) and the combined product fractions evaporated to dryness *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 ml), washed with saturated Na_2CO_3 solution (2 ml), dried over Na_2SO_4, filtered and evaporated to dryness. The residue was treated with Et_2O and evaporated five times to give the title compound as a mixture of diastereomers (m.p. 143-153°C).
TLC: silica gel (90/10/1/1 CH_2Cl_2/MeOH/MoAc/H_2O), R_f=0.58

NMR: consistent with structure
HPLC: 97.5% pure (two diastereomers, 1:1)
M.S.: A molecular ion at m/e = 498.
Anal. Calc'd for $C_{29}H_{30}N_4O_4$:
C, 69.86; H, 6.07; N, 11.24.
Found: C, 69.58; H, 6.12; N, 11.22.

EXAMPLE 83

3(RS)-(2(S)-tert-Butoxycarbonylamino-3-phenylpropanoyl-amino)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodi-azepin-2-one

3(RS)-(2(S)-tert-Butoxycarbonylamino-3-phenyl-propanoylamino)-1,3-dihydro-5-phenyl-2H-1,4-benzodi-azepin-2-one (2.5 gm, 5.01 mmol) was dissolved in DMF (20 ml) cooled to 0°C, treated with a 50% oil dispersion of sodium hydride (241 mg, 5.01 mmol) and stirred 30 minutes. The resulting orange solution was treated with methyl iodide (711 mg, 5.01 mmol) and stirred 1 hour at 25°C. The DMF was removed in vacuo, and the resulting residue treated with dilute Na_2CO_3 (aqueous) and extracted with EtOAc (3x). The organic extracts were combined, washed with H_2O (1x), dried over $MgSO_4$, filtered and evaporated to dryness in vacuo to give a yellow oil (3.57 gm). Flash chromatography on silica gel (15% EtOAc in CH_2Cl_2) gave the title compound as a white foam (1.8 gm) from ether: (m.p. 117-20°C) (soften)).
TLC: Silica GF (180/10/1/1 of CH_2Cl_2/MeOH/H_2O/HoAc R_f=0.48, clean, homogeneous component
NMR: Consistent with structure
HPLC: 98.5% pure (as a 1/1 mixture of diastereomers)
M.S.: Molecular ion at m/e = 512.

Anal. calc'd for $C_{30}H_{32}N_4O_4$:
C, 70.29; H, 6.29; N, 10.93;
Found: C, 69.99; H, 6.32; N, 10.81.

EXAMPLE 84

3(R and S)-(2(S)-Amino-3-phenylpropanoylamino)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

3(RS)-(2(S)-tert-Butoxycarbonylamino-3-phenylpropanoylamino)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (1.8 gm, 3.51 mmol) was dissolved in EtOAc (25 ml), cooled to 0°C, and the solution saturated with HCl (g) over a 10 minute period. After stirring an additional 10 minutes the solvent was removed in vacuo. The solid residue was dissolved in H_2O, basified with saturated Na_2CO_3 (aq.) and extracted with EtOAc (3x). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and stripped to dryness in vacuo to give a grey foam (1.46 gm). Flash chromatography on silica gel (90/10/1/1 of CH_2Cl_2/MeOH/H_2O/HOAc) separated the 1/1 pair of diastereomers into a clean upper (R_f=0.36) and clean lower (R_f=0.24) component. Each component was evaporated to dryness in vacuo, dissolved in CH_2Cl_2, washed with saturated Na_2CO_2 (aq.) (1x), brine (1x), dried over Na_2SO_4 and filtered. The individual filtrates were concentrated to dryness to give the separated diastereomers as white foams (upper component, 605 mg; lower component, 570 mg).

Upper Component(3(S)isomer): (m.p. 92-108°C (shrink and soften))
TLC: Silica gel (90/10/1/1 of CH_2Cl_2/MeOH/H_2O/HoAc) R_f=0.36, single, homogeneous component

NMR: Consistent with structure,
HPLC: Greater than 98.8% single component (100% diastereomerically pure).
M.S.: Molecular ion at m/e = 412
Anal. calc'd for $C_{35}H_{24}N_4O_2$:
C, 72.79; H, 5.87; N, 13.58;
Found: C, 72.79; H, 5.96; N, 13.31.

Lower Component(3(R)isomer): (m.p. 97-108°C (shrink and soften))
TLC: silica gel (90/10/1/1 of CH_2Cl_2/MeOH/H_2O/HoAc)
R_f=0.24, single, homogeneous component
NMR: Consistent with structure.
HPLC: Greater than 99.2% single component (containing less than 0.8% of upper component)
M.S.: Molecular ion at m/e = 412
Anal. calc'd for $C_{25}H_{24}N_4O_2$:
C, 72.79; H, 5.87; N, 13.58;
Found: C, 72.44; H, 5.85; N, 13.48.

EXAMPLE 85

3(R)- and 3(S)-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

3(S)-(2(S)-amino-3-phenylpropanoylamino)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, (Example 84, upper component), (1.15 g, 2.79 mmole) was combined with phenylisothiocyanate (395 mg, 2.93 mmole) in CH_2Cl_2 (20 ml) and the mixture concentrated on a steam bath. The resulting oil was twice diluted with CH_2Cl_2 (20 ml) and both times re-concentrated on the steam bath. The oil was evaporated in vacuo to a foam which was treated with TFA (15 ml) and warmed for 18 minutes in an oil bath

thermostatted at 52°. The TFA was removed in vacuo. The residue was treated twice with CH_2Cl_2 and with Et_2O, evaporated in vacuo after each treatment, and the resulting oil chromatographed on silica gel (90/10/1/1 of CH_2Cl_2/MeOH/H_2O/HoAc). The product fractions were evaporated in vacuo, and the residue was dissolved in CH_2Cl_2, washed with a small volume of 5% NaOH, dried over Na_2SO_4, filtered, and evaporated to give the levorotatory (3(S)) isomer of the title structure.

TLC: Silica gel (90/10/1/1 CH_2Cl_2/MeOH/H_2O/HoAc) R_f=0.31

NMR: Consistent with structure, verifies presence of 0.15 mole of EtOAc

HPLC: Greater than 97.6% pure

M.S.: Molecular ion at m/e = 265

$[\alpha]_D^{25}$ = -236° (0.0033 g/ml, CH_2Cl_2)

Anal. calc'd for $C_{16}H_{15}N_3O$.0.15 H_2O.0.15 $C_4H_{10}O$:
C, 71.43; H, 6.07; N, 15.06;
Found: C, 71.44; H, 5.95; N, 15.11.

3(R)-(2(S)-amino-3-phenylpropanoylamino)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (Example 84, lower component) was converted by the same procedure to the dextrorotatory (3(R) enantiomer of the title compound.

TLC: Silica gel (90/10/1/1 CH_2Cl_2/MeOH/H_2O/HoAc)
R_f=0.31

NMR: Consistent with structure, verifies presence of 0.15 mole of EtOAc

HPLC: Greater than 96.7% pure

M.S.: Molecular ion at m/e = 265

$[\alpha]_D^{25}$ = +227° (0.0033 g/ml, CH_2Cl_2)

Anal. calc'd for $C_{16}H_{15}N_3O.0.15\ H_2O.0.15\ C_4H_{10}O$:
C, 71.43; H, 6.07; N, 15.06;
Found: C, 71.14; H, 5.99; N, 14.90.

EXAMPLE 86

3(R) and 3(S)-Amino-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 82 was carried out using 3-(RS)-amino-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one in place of 3-(RS)-amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one. The product was methylated using the procedure of Example 83 and the resulting methyl derivative was deprotected and separated using the procedure of Example 84. The separated isomers were each treated with phenyl isothiocyanate followed by TFA according to the method of Example 85 giving the 3(R) and 3(S) isomers of the title compound.

3(S) isomer:
TLC: Silica gel (90/10/1/1 CH_2Cl_2/MeOH/H_2O/HoAc), R_f=0.37
NMR: Consistent with structure
HPLC: 95% pure
M.S.: Molecular ion at m/e = 283
$[\alpha]_D^{25}$ = -86.3° (0.0025 g/ml, CH_2Cl_2)

3(R) isomer:
TLC: Silica gel (90/10/1/1 CH_2Cl_2/MeOH/H_2O/HoAc), R_f=0.37
NMR: Consistent with structure
M.S.: Molecular ion at m/e = 283
$[\alpha]_D^{25}$ = +71.4° (0.0028 g/ml, CH_2Cl_2)

EXAMPLE 87

3(S)-(-)-1,3-Dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

3(S)-(-)-3-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (595 mg, 2.24 mmole) was dissolved in CH_2Cl_2 (15 ml) and treated with 2-indolecarbonyl chloride (403 mg, 2.24 mmole) followed by triethylamine (227 mg, 2.24 mmole). The mixture was stirred at room temperature for 30 minutes and concentrated in vacuo. The residue was chromatographed on silica gel (5% Et_2O/CH_2Cl_2) and the combined product fractions evaporated to dryness in vacuo. Three times, Et_2O (15 ml) was added and evaporated in vacuo to give the title compound: (m.p. 168-185°).

TLC: Silica gel (6% Et_2O/CH_2Cl_2), R_f=0.23

NMR: Consistent with structure

HPLC: Greater than 99% pure

M.S.: Molecular ion at m/e = 408

$[\alpha]_D^{25}$ = -103° (0.0078 g/ml, CH_2Cl_2)

Anal. calc'd for $C_{25}H_{20}N_4O_2$

C, 73.51; H, 4.94; N, 13.72;

Found: C, 73.38; H, 4.80; N, 13.66.

EXAMPLE 88

3(S)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(2-indolecarbonylamino)-1-methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 87 was carried out using 3(S)-(-)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one in place of 3(S)-(-)-3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. The title compound was obtained as a foam: (m.p. 162-187°).

TLC: Silica gel (10% Et_2O/CH_2Cl_2) R_f=0.30
NMR: Consistent with structure, verifies presence of 0.2 Et_2O
HPLC: Greater than 99.6% pure
M.S.: Molecular ion at m/e = 426
$[\alpha]_D^{25}$ = +5.57° (0.0031 g/ml, CH_2Cl_2)
Anal. calc'd for $C_{25}H_{19}FN_4O_2 \cdot 0.2C_4H_{10}O$
C, 70.22; H, 4.80; N, 12.70;
Found: C, 70.13; H, 4.75; N, 12.61.

EXAMPLE 89

3(R)-(-)-1,3-Dihydro-5-(2-fluorophenyl)-3-(2-indolecarbonylamino)-1-methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 88 was carried out using 3(R)-(+)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one in place of its 3(S)-(-) isomer. The title compound was obtained as a foam; (m.p. 162-187°)
TLC: Silica gel (10% Et_2O/CH_2Cl_2) R_f=0.30
NMR: Consistent with structure, verifies presence of 0.1 Et_2O
HPLC: Greater than 99.6% pure
M.S.: Molecular ion at m/e = 426
$[\alpha]_D^{25}$ = -5.65° (0.0023 g/ml, CH_2Cl_2)
Anal. calc'd for $C_{25}H_{19}FN_4O_2 \cdot 0.1C_4H_{10}O$
C, 70.31; H, 4.65; N, 12.92;
Found: C, 70.16; H, 4.64; N, 12.86.

EXAMPLE 90

3(R)-(-)-1,3-Dihydro-3-(4-chlorobenzoylamino)-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one

3(R)-(+)-3-Amino-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one (350 mg,

1.24 mmole) was dissolved in CH_2Cl_2 (4 ml) and treated with 4-chlorobenzoyl chloride (217 mg, 1.24 mmole) followed by triethylamine (125 mg, 1.24 mmole). The mixture was stirred at room temperature for 30 minutes and concentrated in vacuo. The residue was chromatographed on silica gel (4% Et_2O/CH_2Cl_2) and the combined product fractions evaporated to dryness in vacuo. Ether was added and removed in vacuo three times, giving the title compound as a foam; (m.p. 113-128°).

TLC: Silica gel (10% Et_2O/CH_2Cl_2) R_f=0.43

NMR: Consistent with structure

HPLC: Greater than 99.6% pure

M.S.: Molecular ion at m/e = 421

$[\alpha]_D^{25}$ = -12.8° (0.0031 g/ml, CH_2Cl_2)

Anal. calc'd for $C_{23}H_{17}ClFN_3O_2$

C, 65.48; H, 4.06; N, 9.96;

Found: C, 65.48; H, 4.17; N, 9.93.

EXAMPLE 91

3(S)-(+)-1,3-Dihydro-3-(4-chlorobenzoylamino)-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 90 was carried out using 3(S)-(-)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one in place of its 3(R)-(+)-isomer. The title compound was obtained as a foam; (m.p. 113-128°).

TLC: Silica gel (10% Et_2O/CH_2Cl_2) R_f=0.43

NMR: Consistent with structure.

HPLC: Greater than 99.6% pure

M.S.: Molecular ion at m/e = 421

$[\alpha]_D^{25}$ = +13.2° (0.0032 g/ml, CH_2Cl_2).

Anal. calc'd for $C_{23}H_{17}ClFN_3O_2$
C, 65.48; H, 4.06; N, 9.96;
Found: C, 65.43; H, 4.09; N, 9.81.

EXAMPLE 92

3(S)-(-)-1,3-Dihydro-3-(4-bromobenzoylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

3(S)-(-)-3-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (35 mg, 0.132 mmole) was dissolved in CH_2Cl_2 (1 ml) and treated with 4-bromobenzoylchloride (29 mg, 0.132 mmole) followed by triethylamine (13.3 mg, 10.132 mmole). The mixture was stirred at room temperature for 30 minutes and concentrated in vacuo. The residue was chromatographed on silica gel (3% Et_2O/CH_2Cl_2) and the combined product fractions evaporated to dryness in vacuo. Ether was added and removed in vacuo three times, giving the title compound as a foam; (m.p. 120-133°).

TLC: Silica gel (7% Et_2O/CH_2Cl_2), R_f=0.36
NMR: Consistent with structure
HPLC: Greater than 99.1% pure
M.S.: Molecular ion at m/e 447
$[\alpha]_D^{25}$ = -72.4° (0.0027 g/ml, CH_2Cl_2).
Anal. calc'd for $C_{23}H_{18}BrN_3O_2$
C, 61.62; H, 4.05; N, 9.37;
Found: C, 61.94; H, 4.07; N, 9.20.

EXAMPLE 93

3(R)-(+)-1,3-Dihydro-3-(4-bromobenzoylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 92 was carried out using 3(R)-(+)-3-amino-1,3-dihydro-1-methyl-5-phenyl-

2H-1,4-benzodiazepin-2-one in place of its 3(S)-(-) isomer. The title compound was obtained as a foam; (m.p. 120-133°)

TLC: Silica gel (7% Et_2O/CH_2Cl_2); R_f=0.36

NMR: Consistent with structure

HPLC: Greater than 99.2% pure

M.S.: Molecular ion at m/e = 447

$[\alpha]_D^{25}$ = +75.1° (0.0022 g/ml, CH_2Cl_2).

Anal. calc'd for $C_{23}H_{18}BrN_3O_2$

C, 61.62; H, 4.05; N, 9.37;

Found: C, 62.00; H, 4.12; N, 9.27.

EXAMPLE 94

3(R)-(+)-1,3-Dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 87 was carried out using 3(R)-(+)-3-amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one in place of its 3(S)-(-) isomer. The title compound was obtained as a foam; (m.p. 168-185°).

TLC: Silica gel (6% EtO/CH_2Cl_2); R_f=0.23

NMR: Consistent with structure

HPLC: Greater than 99.2% pure

M.S.: Molecular ion at m/e = 408

$[\alpha]_D^{25}$ = +100° (0.0052 g/ml, CH_2Cl_2).

Anal. calc'd for $C_{25}H_{20}N_4O_2$

C, 73.51; H, 4.94; N, 13.72;

Found: C, 73.16; H, 4.88; N, 13.53.

EXAMPLE 95

Z-1,3-Dihydro-1-methyl-5-phenyl-3-(3-thienylmethylene)-2H-1,4-benzodiazepin-2-one and E-1,3-Dihydro-1-methyl-5-phenyl-3-(3-thienylmethylene)-2H-1,4-benzodiazepin-2-one

To a cooled (-60°C) solution of diisopropylamine (0.84 ml, 6.0 mmol) in THF (10.2 ml) was added 1.5M butyllithium in hexane (4.0 ml, 6.0 mmol). The solution was stirred 10 min. at -60°C and then warmed to 25°C. The light yellow solution was recooled to -60°C and treated with solid 1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (75 mg, 3.0 mmol) portionwise (5 x 15 mg). The reaction was permitted to warm to 0°C and then recooled to -60°C. A solution of thiophene-3-carboxaldehyde (336 mg, 3.0 mmol) in THF (6 ml) was added to the deep red anion solution, the cooling bath was removed, and the reaction allowed to warm to 25°C. The reaction was quenched with brine and extracted with ether (3X). The combined extracts were washed with H_2O (1X), dried over $MgSO_4$, filtered, and stripped to dryness in vacuo. The crude red oil was chromatographed on silica gel (10% Et_2O in CH_2Cl_2) to give the intermediate alcohol as a buff-colored solid: 210 mg, m.p. 188-9°C. TLC: silica GF (10% Et_2O in CH_2Cl_2) single homogeneous component. A portion of this product (171 mg, 0.472 mmol) was refluxed in a mixture of trifluoroacetic acid (3 ml) and trifluoroacetic anhydride (1 ml) for 12 hrs. The solvent was removed in vacuo and the residue was treated with H_2O, basified with 10% NaOH (aq) and extracted with ether (3X). The combined extracts were washed with H_2O

(1X), dried over $MgSO_4$, filtered and stripped to dryness in vacuo to give a crude oil. Chromatography on silica gel (2% Et_2O in CH_2Cl_2) provided the title compounds which were obtained as light yellow solids from ether.

Z-isomer: (m.p. 196-197°C).
TLC: Silica GF (4% Et_2O in CH_2Cl_2), R_f = 0.37, single homogeneous component.
PMR: Consistent with the title structure.
HPLC: Greater than 99.8% pure.
M.S.: Mol. ion = 344 m/e.
Anal. calc'd for $C_{21}H_{16}N_2OS$:
C, 73.23; H, 4.68; N, 8.13;
Found: C, 73.37; H, 4.78; N, 7.79.

E-isomer: (m.p. 194-196°C).
TLC: Silica GF (4% Et_2O in CH_2Cl_2), R_f = 0.28 single homogeneous component.
PMR: Consistent with the title structure.
HPLC: Greater than 99.9% pure.
M.S.: Mol. ion = 344 m/e.
Anal. calc'd for $C_{21}H_{16}N_2OS$:
C, 73.23; H, 4.68; N, 8.13;
Found: C, 73.12; H, 4.83; N, 7.73.

EXAMPLE 96

3(RS)-(BOC-D-tryptophyl)amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 77 was carried out using BOC-D-tryptophan in place of BOC-L-tryptophan. The chromatographed product was crystallizd from Et_2O and dried in vacuo at 80°: (m.p. 171-174° (↑)).

TLC: A single spot (R_f = 0.56, silica gel plate, 10% (v/v) CH_3OH in CH_2Cl_2).
NMR: The spectrum was consistent with the title structure and verified the presence of two diastereomers.
HPLC: Greater than 98.4% pure (68.9% and 29.5%).
Anal. calc'd for $C_{31}H_{31}N_5O_4$:
C, 69.25; H, 5.81; N, 13.03;
Found: C, 69.24; H, 6.03; N, 13.04.

EXAMPLE 97

3(RS)-[4-(3-Indole)butyrylamino]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 77 was carried out using 4-(3-indolyl)butyric acid (0.082 g, 0.4 mmol) in place of BOC-L-tyrptophan. The product was chromatographed as in Example 75, crystallized from a mixture of acetone (1 ml) and ether (3 ml), and dried in vacuo at 80°: (m.p., 258-259°).
NMR: The spectrum was consistent with the title structure.
HPLC: 98.9% pure.
MS: A molecular ion at m/e = 436.
Anal. calc'd for $C_{27}H_{24}N_4O_2$:
C, 74.29; H, 5.54; N, 12.84;
Found: C, 74.39; H, 5.65; N, 12.93.

EXAMPLE 98

1,3-Dihydro-3(RS)-(benzyloxycarbonyl)aminomethyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepine

To a magnetically stirred solution of 1,3-dihydro-3(RS)-benzyloxycarbonyl)aminomethyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-thione (1.85

g, 4.3 mmol) in 150 ml of ethanol were added, at room temperature, three portions of freshly prepared Raney nickel (slurried in ethanol, approximately 4-5 g). The resulting reaction mixture was stirred vigorously overnight and treated with an additional equal portion of Raney nickel. After 50 hours of total reaction time, the suspension was filtered carefully; the residual Raney nickel was washed copiously with ethanol. Concentration of the filtrate under reduced pressure gave 880 mg of product essentially homogeneous by TLC (ethyl acetate-hexane 1:1 v/v). The analytical sample was obtained via silica gel chromatography (chloroform-methanol 96:4) as a foam. TLC, HPLC greater than 97% pure.

NMR ($CDCl_3$): Consistent with the title structure.

MS (14 ev): 403 (M^+), 295, 253, 239, 219.

Anal. calc'd for $C_{24}H_{22}FN_3O_2 \cdot 0.03\ CHCl_3$:

N, 10.32; C, 70.90, H, 5.45;

Found: N, 10.16; C, 70.89; H, 5.60.

EXAMPLE 99

1,3-Dihydro-3(RS)-[3'-(thiophene)carbonyl]amino-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepine

1,3-Dihydro-3(RS)-aminomethyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepine hydrobromide (300 mg, 0.59 mmol) and 3-thiophenecarboxylic acid chloride (150 mg, 1.02 mmol) were combined in 50 ml of methylene chloride. The reaction mixture was immersed in an ice bath and treated with triethylamine (330 µl, 2.36 mmol). After addition was complete, stirring was continued at 0°C for 10 min. more and then at room temperature for 15 min. The reaction mixture was partitioned between

methylene chloride and saturated sodium bicarbonate solution. The phases were separated and the organic layer was washed with brine, then dried ($MgSO_4$) and concentrated under reduced pressure. The crude product (300 mg) was purified via silica gel chromatography (chloroform - methanol - ammonia, 95:5:0.5 v/v, elution) to give the analytical sample.
NMR ($CDCl_3$): Consistent with the title structure.
MS (14 ev): 379 (M^+)
Anal. calc'd for $C_{21}H_{18}FN_3OS.0.1\ CHCl_3$:
N, 10.74; C, 64.75; H, 4.66;
Found: N, 10.45; C, 64.51; H, 4.82.

EXAMPLE 100

1,3-Dihydro-3(RS)-(2'-indolecarbonyl)aminomethyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepine Solvate

1,3-Dihydro-3(RS)-aminomethyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepine hydrobromide (300 mg, 0.59 mmol) and 2-indole carboxylic acid chloride (127 mg, 0.70 mmol) were combined in 30 ml of methylene chloride. The reaction mixture was immersed in an ice bath and treated with triethylamine (330 µl, 2.36 mmol). After addition was complete, stirring was continued at 0°C for 10 min. more and then at room temperature for 15 minutes. The reaction mixture was partitioned between methylene chloride and saturated sodium bicarbonate solution. The phases were separated and the organic layer was washed with brine, then dried ($MgSO_4$) and concentrated under reduced pressure. The crude product (220 mg) was purified via silica gel chromatography (chloroform - methanol elution, 95:5 v/v) to give the analytical sample.

NMR ($CDCl_3/CD_3OD$): Consistent with the title structure.
MS (14 ev): 412 (M^+), 252, 239.
Anal. calc'd for $C_{25}H_{21}FN_4O.0.15\ CHCl_3$:
N, 13.01; C, 70.19; H, 4.95;
Found: N, 12.70; C, 70.19; H, 5.18.

EXAMPLE 101

1,3-Dihydro-3(RS)-(2-L-hydroxy-2-phenylacetyl)aminomethyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepine

1,3-Dihydro-3(RS)-aminomethyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepine hydrobromide (300 mg, 0.59 mmol) and L-mandelic acid (134 mg, 0.88 mmol) were combined in 5 ml of dimethylformamide and treated with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (169 mg, 0.88 mmol). The pH of the resulting reaction mixture was adjusted to 8.5 with triethylamine and the reaction was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (60ml). The organic phase was then washed in succession with sodium bicarbonate solution (3 x 50 ml) and brine. The dried ($MgSO_4$) extracts were concentrated to give 200 mg of crude product as a mixture of diastereomers. Preparative thick layer chromatography (chloroform - ethanol - ammonia elution, 90:10:1 v/v) afforded the less polar, faster moving component as a homogeneous analytical sample.
HPLC: Greater than 98% pure.
NMR ($CDCl_3$): Consistent with the title structure.
MS (14 ev): 403 (M^+), 252, 239,212.
Anal. calc'd for $C_{24}H_{22}FN_3O_2.0.5\ H_2O$
N, 10.18; C, 69.82; H, 5.62;
Found: N, 9.67; C, 69.81; H, 5.55.

EXAMPLE 102

1-(2-Cyanoethyl)-1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one (A, 85%) and 1-(2-cyanoethyl)-1,3-dihydro-5-(2-fluorophenyl)-3(R)-[1'-(2-cyanoethyl)-3'-indolyl]-methyl-2H-1,4-benzodiazpin-2-one (B, 15%)

The procedure of Example 4 was carried out using acrylonitrile (0.12 g, 2,3 mmol) in place of methyl iodide. The chromatographed product, a mixture of A (85%) and B (15%) was dried in vacuo at 90°: (m.p. 97-105° (↑)).

NMR: The spectrum was consistent with the 85:15 mixture of the title structure and showed the presence of 0.9 mol of DMF.

HPLC: 96.4% (82.4% + 14.0%).

TLC: A single spot (R_f = 0.22, silica gel plate, 5% (v/v) Et_2O in CH_2Cl_2).

MS: Molecular ions at m/e=436 and 489.

Anal. calc'd for 0.85 $C_{27}H_{21}FN_4O$ + 0.15 $C_{30}H_{24}FN_5O$.0.9 C_3H_7NO:

C, 71.07; H, 5.35; N, 13.88;

Found: C, 70.95; H, 5.18; N, 13.63.

EXAMPLE 103

1-(2-Carboxyethyl)-1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 4 was carried out using ethyl acrylate (0.22 g, 2.2 mmole) in place of methyl iodide. The chromatographed product was evaporated in vacuo, dissolved in methanol (5 ml), treated with sodium hydroxide (0.91 ml of 1 M solution), and stirred at room temperaure for 24 hours. The mixture was evaporated in vacuo, and

the residue was dissolved in water (10 ml), washed with ether (10 ml), acidified with 1 N HCl, and extracted with CH_2Cl_2 (3 x 10 ml). The CH_2Cl_2 layers were washed with water (1 x 10 ml), dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel (180:5:1:1 followed by 180:10:1:1 (v/v/v/v) CH_2Cl_2:CH_3OH:HoAc:H_2O) and the product evaporated to dryness in vacuo. The residue was dried in vacuo at 40°: (m.p. ~75-90° foam, ~130-160° melt).

TLC: A single spot (R_f = 0.32, silica gel plate, 180:10:1:1 (v/v/v/v) CH_2Cl_2:CH_3OH:HOAc:H_2O).

NMR: The spectrum was consistent with the title structure and verified the presence of ether.

HPLC: 99.6% pure.

MS: A molecular ion at m/e = 455.

Anal. calc'd for $C_{27}H_{22}FN_3O_3$.0.55 $C_4H_{10}O$.0.35 H_2O):

C, 69.78; H, 5.66; N, 8.36;

Found: C, 69.72; H, 5.29; N, 8.07.

EXAMPLE 104

1,3-Dihydro-3(R)-(3'-indolyl)methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one-4-oxide

1,3-Dihydro-3(R)-(3'-indolyl)methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (300 mg, 0.78 mmol) and m-chloroperoxybenzoic acid (85%) (156 mg, 0.90 mmol) were combined at room templerature in 20 ml of chloroform. The reaction mixture was allowed to stand at room temperarure overnight, then was diluted with 30 ml of chloroform and washed with cold, saturated sodium bicarbonate solution. The

combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated to afford 310 mg of crude product. Silica gel chromatography (hexane-ethyl acetate, 1:2 v/v) provided the analytical sample.

HPLC: 99% pure.

NMR ($CDCl_3$): Consistent with the title structure.

MS (14 ev): 415, 397, 369, 267.

Anal. calc'd. for $C_{24}H_{18}FN_3O_2.1.0\ CHCl_3$

N, 8.10; C, 57.87; H, 3.69;

Found: N, 8.09; C, 58.14; H, 3.82.

EXAMPLE 105

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-(2-indolecarbonyl amino)-2H-1,4-benzodiazepin-2-one

3-(RS)-Amino-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (1.5 gm, 5.57 mmol), indole-2-carbonyl chloride (1.05 gm, 5.85 mmol) and triethylamine (0.814 ml, 5.85 mmol) were combined in CH_2Cl_2 (15 ml) and stirred 10 min. The reaction was concentrated and chromatographed on silica gel (5% MeOH in CH_2Cl_2) to give the title compound as a white solid from CH_2Cl_2: (m.p. 290-291°).

TLC: Silica GF (5% MeOH in CH_2Cl_2), single homogeneous component.

NMR: Consistent with title structure and verifies the presence of 0.16 CH_2Cl_2.

HPLC: Greater than 99% pure.

M.S.: Mol. ion = 412 m/e (free base).

Anal. calc'd for $C_{24}H_{17}FN_4O_2.0.16\ CH_2Cl_2$:

C, 68.11; H, 4.10; N, 13.15;

Found: C, 68.06, H, 4.12; N, 12.91.

EXAMPLE 106

1,3-Dihydro-3-(RS)-(4-nitrophenylcarbonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-3-(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (100 mg, 0.37 mmol) and p-nitrobenzoic acid (70 mg, 0.41 mmol) were combined at room temperature in 5 ml of methylene chloride. To this reaction mixture was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (79 mg, 0.41 mmol). The pH of the reaction mixture was then adjusted to 8.5 with triethylamine and stirring was continued at room temperature overnight. The reaction mixture was partitioned between methylene chloride and 10% citric acid solution. The phases were separated and the organic layer was washed in succession with 10% citric acid solution (1 x 30 ml), saturated sodium bicarbonate solution (2 x 30 ml) and brine. The dried ($MgSO_4$) extracts were concentrated to yield 83 mg of crude product. Preparative thick layer chromatography (chloroform - methanol - ammonia, 96:4:0.4 v/v) afforded the analytical sample (70 mg).

HPLC: Greater than 96.5% pure.

NMR ($CDCl_3$): Consistent with the title structure.

MS (14 ev): 418 (M^+), 268, 252.

Anal. calc'd for $C_{22}H_{15}FN_4O_4 \cdot 0.1\ CHCl_3$

N, 13.02; C, 61.68; H, 3.54;

Found: N, 12.66; C, 61.94; H, 3.74.

EXAMPLE 107

1,3-Dihydro-3-(RS)-(2-indolecarbonyloxy)-5-phenyl-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-3-(RS)-hydroxy-5-phenyl-2H-1,4-benzodiazepin-2-one (100 mg, 0.398 mmol) was dissolved in CH_2Cl_2 (10 ml), treated with indole-2-carbonyl chloride (78.6 mg, 0.438 mmol) and 4-dimethylaminopyridine (DMAP, 53.5 mg, 0.438 mmol) and stirred 16 hrs. at 25°C. A second portion of indole-2-carbonylchloride (78.6 mg, 0.438 mmol and DMAP (53.5 mg, 0.438 mmol) was added and the reaction stirred an additional 24 hrs. Chromatography of the reaction mixture on silica gel (1% MeOH in CH_2Cl_2) gave the title compound (100 mg) as a white solid from MeCN: (m.p. 271-273°).
TLC: Silca GF (4% MeOH in CH_2Cl_2), R_f = 0.41, single homogeneous component.
NMR: Consistent with title structure.
HPLC: Greater than 98.6% pure.
MS: Molecular ion at m/e=395.
Anal. calc'd for $C_{24}H_{17}N_3O_3$:
C, 72.90; H, 4.33; N, 10.63;
Found: C, 72.70; H, 4.31; N, 10.64.

EXAMPLE 108

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-(3-thiophene carbonylamino)-2H-1,4-benzodiazepin-2-one

3-(RS)-Amino-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (75 mg, 0.229 mmol), thiophene-3-carbonyl chloride (44.9 mg, 0.306 mmol) and triethylamine (42.5 µl, 0.306 mmol) were combined in CH_2Cl_2 (4 ml) and stirred 10 min. at 25°C. The reaction was concentrated and chromatographed on

silica gel (2% MeOH in CH_2Cl_2) to give the title compound as a white solid from Et_2O: (m.p. 238-239°).

TLC: Silica GF (5% MeOH in CH_2Cl_2), R_f = 0.36, single homogeneous component.

NMR: Consistent with title structure and verifies the presence of .05 $(C_2H_5)_2O$ and 0.70 H_2O).

HPLC: Greater than 98.8% pure.

MS: Mol. ion = 379 m/e (free base).

Anal. calc'd for $C_{20}H_{14}FN_3O_2S$. .05 $(C_2H_5)_2O$.0.70 H_2O:

C, 61.30; H, 4.05; N, 10.62;

Found: C, 61.24; H, 3.68; N, 10.57.

EXAMPLE 109

1,3-Dihydro-3-(RS)-(3-indolecarbonylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one

3-(RS)-Amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (49.2 mg, 0.196 mmol), indole-3-carboxylic acid (37.9 mg, 0.235 mmol) and 1M DCC in CH_2Cl_2 solution (0.235 ml, 0.235 mmol) were mixed in DMF (2 ml) and the pH adjusted to 9.0 with triethylamine (32.7 µl, 0.235 mmol). The reaction was stirred 18 hrs. at 25°C, the DMF removed in vacuo, and the residue chromatographed on a Waters Semi-Prep C-18 30 x 0.9 cm column (gradient elution of 5 to 95% CH_3CN in H_2O) to give the title compound as a white solid from MeOH/ether: (m.p. 265-268°).

TLC: Silica GF (90/10/1/1 of CH_2Cl_2/MeOH/H_2O/HOAc), R_f = 0.57, single homogeneous component.

NMR: Consistent with title structure and verifies the presence of 2.0 CH_3OH.

HPLC: 100% pure.
MS: Mol. ion = 394 m/e (free base).
Anal. calc'd for $C_{24}H_{18}N_4O_2.2CH_3OH$:
C, 68.10; H, 5.72; N, 12.22;
Found: C, 68.19; H, 4.62; N, 12.50.

EXAMPLE 110

1,3-Dihydro-3-(RS)-(4-thianaphtheneacetyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-3-(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (100 mg, 0.37 mmol) and 4-thianaptheneacetic acid (79 mg, 0.41 mmol) were combined at room temperature in 5 ml of methylene chloride. To this reaction mixture was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (79 mg, 0.41 mmole). The pH of the reaction mixture was then adjusted to 8.5 with triethylamine and stirring was continued at room temperature overnight. The reaction mixture was partitioned between methylene chloride and 10% citric acid solution. The phases were separated and the organic layer was washed in succession with 10% citric acid solution (1 x 30 ml), saturated sodium bicarbonate solution (2 x 30 ml) and brine. The dried ($MgSO_4$) extracts were concentrated to yield 130mg of crude product. Preparative thick layer chromatography (chloroform - methanol - ammonia, 95:5:0.5 v/v) afforded the analytical sample, m.p. 259-260°C.

NMR ($CDCl_3$): consistent with the title structure.
MS (14 ev): 443 (M^+), 268, 174.
Anal. calc'd for $C_{25}H_{18}FN_3O_2S.0.075\ CHCl_3$
N, 9.28; C, 66.56; H, 4.02;
Found: N, 9.10; C, 66.53; h, 4.11.

EXAMPLE 111

1,3-Dihydro-3-(RS)-(4-chlorophenylcarbonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-3-(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (100 mg, 0.37 mmol) and p-chlorobenzoyl chloride (52 µl, 0.41 mmole) were combined at room temperature in 5 ml of methylene chloride. The resulting solution was protected from moisture and stirred at room temperature overnight. The reaction mixture was diluted with 70 ml of methylene chloride and washed with sodium bicarbonate solution (sat.) and brine. The organic extracts were dried ($MgSO_4$) and concentrated to give 150 mg of crude product. Chromatography on silica gel (chloroform - methanol - ammonia; 95:5:0.5 v/v) and trituration with hexane yielded the analytical product as a white powder, m.p. 258-259°C.

HPLC: Greater than 98% pure.

NMR: ($CDCl_3$): Consistent with the title structure.

MS (14 ev): 407 (M^+), 268, 252, 241.

Anal. calc'd for $C_{22}H_{15}ClFN_3O_2 \cdot 0.2\ CHCl_3$

N, 9.73; C, 61.76; H, 3.55;

Calc'd: N, 9.34; C, 61.65; H, 3.68.

EXAMPLE 112

1,3-Dihydro-3-(RS)-(4-methylphenylsulfonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-3-(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (116 mg, 0.43 mmole) and p-toluenesulfonyl chloride (82 mg, 0.43 mmole) were combined at room temperature in 5 ml of methylene chloride. The pH of the reaction mixture was then adjusted to 8.5 with triethylamine and stirring was

continued at room temperature overnight. The reaction mixture was partitioned between methylene chloride and 10% citric acid solution. The phases were separated and the organic layer was washed in succession with 10% citric acid solution (1 x 30 ml), saturated sodium bicarbonate solution (2 x 30 ml) and brine. The dried ($MgSO_4$) extracts were concentrated to yield 200 mg of crude product. Recrystallization from ethyl acetate afforded the analytical sample as white needles, m.p. 215-216°C.

HPLC: Greater than 99% pure.

NMR ($CDCl_3$): Consistent with the title structure.

MS (14 ev): 359, 316, 268, 241, 225, 212, 92.

Anal. calc'd for $C_{22}H_{18}FN_3O_3S.0.1C_4H_8O_2$

N, 9.72; C, 62.23; H, 4.38;

Found: N, 9.64; C, 61.92 H, 4.31.

EXAMPLE 113

1-Carboxymethyl-1,3-dihydro-5-(2-fluorophenyl)-3(RS)-(2-indolecarbonylamino)-2H-1,4-benzodiazepin-2-one

The procedure of Example 4 was carried out using 1,3-dihydro-5-(2-fluorophenyl)-3(RS)-(2-indolecarbonylamino)-2H-1,4-benzodiazepin-2-one (0.92 g, 2.2 mmole) in place of 1,3-dihydro-5-(2-fluorophenyl)-3-(R)-(3'-indolyl)-methyl-2H-1,4-benzodiazepin-2-one, and ethyl bromoacetate (0.38 g, 2.25 mmol) in place of methyl iodide. The chromatographed product (10% ether in CH_2Cl_2) (0.05 g, 0.098 mmol) and sodium hydroxide (0.14 ml, 1N, 0.14 mmol) were stirred together in CH_3OH (3 ml) at room temperature for 36 hours. The mixture was concentrated in vacuo, diluted to 5 ml with H_2O, made acidic with 1 N HCl, and extracted with CH_2Cl_2 (3 x 5 ml). The organic

layers were combined, washed with water (1 x 5 ml), dried over Na_2SO_4, filtered, and evaporated to dryness in vacuo. The residue was crystallized from acetone (0.1 ml) and Et_2O (2 ml) and the solid dried in vacuo at 60°; (m.p. 278-278.5° (d)).
TLC: A single spot (R_f = 0.27, silica gel plate, 180:10:1:1 (v/v/v/v) CH_2Cl_2:CH_3OH:HOAc:H_2O).
NMR: The spectrum was consistent with the title structure and verified the presence of ether and acetone.
HPLC: 99.4% pure.
MS: A molecular ion at m/e = 470.
Anal. calc'd for $C_{26}H_{19}FN_4O_4 \cdot 0.6C_3H_6O \cdot 0.2C_4H_{10}O \cdot 0.8\ H_2O$:
C, 64.25; H, 4.94; N, 10.48;
Found: C, 64.29; H, 4.56; N, 10.23.

EXAMPLE 114

1,3-Dihydro-3-(RS)-(5-fluoroindole-2-carbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

3-(RS)-Amino-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (100 mg, 0.398 mmol) was suspended in 2 ml of methylene chloride. 5-fluoro-indole-2-carboxylic acid chloride (87 mg, 0.438 mmol) was added to the methylene chloride suspension. The pH of the stirred mixture was adjusted to 9 with 100 µl of triethylamine. The reaction mixture was stirred for 24 hours. The mixture was then diluted with 1 ml of methanol and filtered. The filtrate was pipeted onto a 2000 µ Analtech preparative TLC plate which was developed in a 95:5:0.5 chloroform, methanol, water (CMW) solvent system. The product band was collected. The silica was washed with

90:10:1 CMW. The filtrate was evaporated and the residue was dissolved in methanol and placed in a small vial. The solvent was evaporated to yield 15.2 mg of product.

HPLC: 90% pure.

MS: M^+ (14 ev), m/e 430.

NMR: Consistent with title product.

Anal. calc'd for $C_{24}H_{16}F_2N_4O_2$ $1.6CH_3OH$
N, 11.63; C, 63.83; H, 4.65;
Found: N, 11.66; C, 63.84; H, 3.72.

EXAMPLE 115

1,3-Dihydro-3-(RS)-(3'-methylindenyl-2-carbonyl)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-3-(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (100 mg, 0.37 mmol) and 3-methylindene-2-carboxylic acid (70 mg, 0.40 mmol) were combined at room temperature in 5 ml of methylene chloride. To this reaction mixture was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (80 mg, 0.41 mmol). The pH of the reaction mixture was then adjusted to 8.0 with triethylamine and stirring was continued at room temperature overnight (19 hours). The reaction mixture was partitioned between methylene chloride and 10% citric acid solution. The phases were separated and the organic layer was washed in succession with 10% citric acid solution (1 x 30 ml), saturated sodium bicarbonate solution (2 x 30 ml), and brine. The dried ($MgSO_4$) extrcts were concentrated to yield 130 mg of crude product. Preparative thick layer chromatography (hexane - ethyl acetate, 1:1 v/v) afforded the analytical sample.

HPLC: Greater than 98% pure.
NMR ($CDCl_3$): Consistent with the title structure.
MS (14 ev): 425 (M^+), 268, 199, 156.
Anal. calc'd for $C_{26}H_{20}FN_3O_2.1.25\ H_2O$
N, 9.38; C, 69.70; H, 5.06;
Found: N, 8.86; C, 69.75; H, 4.85.

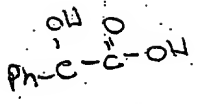
EXAMPLE 116

1,3-Dihydro-3-(RS)-(2-quinaldyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (100 mg, 0.37 mmol) and 2-quinoline carboxylic acid (quinaldic acid) (70 mg, 0.40 mmol) were combined at room temperature in 5 ml of methylene chloride. To this reaction mixture was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (76 mg, 0.40 mmole). The pH of the reaction mixture was then adjusted to 8.5 with triethylamine and stirring was continued at room temperature for 48 hours. The reaction mixture was partioned between methylene chloride and 10% citric acid solution. The phases were separated and the organic layer was washed in succession with 10% citric acid solution (1 x 30 ml), saturated sodium bicarbonate solution (2 x 30 ml) and brine. The dried ($MgSO_4$) extracts were concentrated to yield 150 mg of crude product. Preparative thick layer chromatography (chloroform - methanol - ammonia, 97:3:0.3 v/v) afforded the analytical sample (60 mg).
NMR ($CDCl_3$): Consistent with the title structure.
MS (14 ev): 424 (M^+), 268, 241, 198, 184.
Anal. calc'd for $C_{25}H_{17}FN_4O_2.0.75\ H_2O$
N, 12.79; C, 68.56; H, 4.25;
Found: N, 13.35; C, 68.53; H, 4.23.

EXAMPLE 117

1,3-Dihydro-3-(RS)-(2-L-hydroxy-2-phenylacetyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one



1,3-Dihydro-3-(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (100 mg, 0.37 mmol) and L-mandelic acid (63 mg, 0.41 mmol) were combined at room temperature in 10 ml of methylene chloride. To this reaction mixture was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (79 mg, 0.41 mmol). The pH of the reaction mixture was then adjusted to 8.5 with triethylamine and stirring was continued at room temperature for 96 hours. The reaction mixture was partitioned between methylene chloride and 10% citric acid solution. The phases were separated and the organic layer was washed in succession with 10% citric acid solution (1 x 30 ml), saturated sodium bicarbonate solution (2 x 30 ml) and brine. The dried ($MgSO_4$) extracts were concentrated to yield 130 mg of crude product as a mixture of diastereomers. Preparative thick layer chromatography (chloroform - methanol - ammonia, 95:5:0.5, v/v) afforded the analytical sample. NMR ($CDCl_3$): consistent with the title structure.

EXAMPLE 118

1,3-Dihydro-3-(RS)-(5-Chloroindole-2-carbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

3-(RS)-Amino-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (100 mg, 0.391 mmol) was suspended in 2 ml of methylene chloride. 5-Chloroindole-2-carboxylic acid chloride (86.7 mg, 0.438 mmol) was added. The pH of the stirred mixture was adjusted to 9 with triethylamine (95 µl). The

reaction mixture was stirred for 24 hours. The mixture was then diluted with 1 ml of methanol and filtered. The filtrate was pipeted onto a 2000 μ Analtech preparative TLC plate which was developed in a 95:5:0.5 chloroform, methanol, water (CMW) solvent system. The product band was collected. The silica was washed with 90:10:1 CMW. The filtrate was evaporated and the residue was dissolved in methanol and placed in a small vial. The solvent was evaporated to yield 16.4 mg of purified product.

HPLC: 90% pure.

MS (14 ev): (M^+) m/e 446.

NMR: Consistent with title product.

Anal. calc'd for $C_{24}H_{16}Cl_1FN_4O_2 \cdot 0.8CH_3OH$

C, 63.04; H, 4.09; N, 11.86;

Found: C, 63.03; H, 3.66; N, 11.58.

EXAMPLE 119

3-(RS)-[N-(2-indolecarbonyl)-N-methylamino]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-3-(RS)-methylamino-5-phenyl-2H-1,4-benzodiazepin-2-one (130 mg, 0.49 mmol) and indole-2-carbonyl chloride (88 mg, 0.49 mmol) were combined in CH_2Cl_2 (5 ml) and stirred 2 hours at 25°C. The reaction was concentrated and chromatographed on silica gel (3% MeOH in CH_2Cl_2) to give the title compound as a white solid from CH_2Cl_2: (m.p. 287-288.5°).

TLC: Silca GF (5% MeOH in CH_2Cl_2), R_f = 0.41, single homogeneous component.

NMR: Consistent with title structure and verified the presence of 0.25 H_2O.

HPLC: Greater than 97.2% pure.
MS: Mol. ion = 408 m/e (free base).
Anal. calc'd for $C_{25}H_{20}N_4O_2.0.25H_2O$
C, 72.70; H, 5.00; N, 13.57;
Found: C, 72.64; H, 4.87; N, 13.30.

EXAMPLE 120

1,3-Dihydro-3-(RS)-(5-Bromoindole-2-carbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

The procedure of Example 114 was carried out using 5-bromoindole-2-carboxylic acid chloride (113 mg, 0.438 mmole) in place of 5-fluoroindole-2-carboxylic acid chloride.
HPLC: 82% pure.
MS: M^+ (14 ev) , m/e 490.
NMR: Consistent with title product.
Anal. calc'd for $C_{24}H_{16}BrFN_4O_2 .0.28CHCl_3$
N, 10.68; C, 55.57; H, 3.13;
Found: N, 10.31; C, 55.98; H, 3.36.

EXAMPLE 121

3-(RS)-Cinnamoylamino-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

3-(RS)-Amino-1,3-dihydro-5-(2'-fluorophenyl)-2H-1,4-benzodiazepin-2-one (50 mg, 0.186 mmol) was suspended in methylene chloride (1 ml). Cinnamoyl chloride (34.5 mg, 0.207mmol) was added to the methylene chloride mixture. The pH of the stirred mixture was adjusted to 9 with 50 µl of triethylamine. After stirring for 16 hours the mixture was filtered. The product in the filtrate was purified by prep TLC. The product band was collected by washing the silica containing the

product, with 80:20:2 CMW. The solvent was evaporated and the residue was dissolved in methanol, placed in a small vial and evaporated. Yield 16.6 mg.
HPLC: 97% pure.
MS: M^+ (14 ev) m/e 399
NMR: Consistent with title structure.
Anal. calc'd for $C_{24}H_{18}FN_3O_2 \cdot 0.126CHCl_3$
N, 10.18; C, 70.24; H, 4.42;
Found: N, 10.08; C, 70.07; H, 4.46.

EXAMPLE 122

1,3-Dihydro-3-(RS)-(5-hydroxy-2-indolylcarbonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-3-(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (100 mg, 0.37 mmole) and 5-hydroxyindole-2-carboxylic acid (75 mg, 0.44 mmole) were combined at room temperature in a mixture of 1 ml of dimethylformamide and 5 ml of methylene chloride. To this reaction mixture was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (76 mg, 0.40 mmol). The pH of the reaction mixture was then adjusted to 8.5 with triethylamine and stirring was continued at room temperature for 48 hours. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and 10% citric acid solution. The phases were separated and the organic layer was washed in succession with 20% citric acid solution (1 x 30 ml), saturated sodium bicarbonate solution (2 x 30 ml) and brine. The dried ($MgSO_4$) extracts were concentrated to yield 200 mg of the product. Preparative thick layer chromatography (chloroform - ethanol - ammonia, 90:10:1, v/v) afforded the analytical sample (80 mg).

NMR (CD_3OD): Consistent with the title structure.
MS (14 ev): 428 (M^+), 227, 176, 159.
Anal. calc'd. for $C_{24}H_{17}FN_4O_3 \cdot 0.25\ CHCl_3$
N, 12.23; C, 63.56; H, 3.79;
Found: N, 12.09; C, 63.99; H, 4.09.

EXAMPLE 123

1-Carboxamidomethyl-1,3-dihydro-3R-(3-indolylmethyl)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-3R-(3-indolylmethyl)-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (10 g, 26 mmol) was stirred in 120 ml of degassed DMF at 0°C under nitrogen with sodium hydride (1.25 g, 26 mmol) until homogeneous (1 hour). Ethylbromoacetate (2.88 ml, 26 mmol) was added and the reaction mixture was stirred at room temperature for 1 hour. The reaction was quenched in 1 l of water. The aqueous solution was extracted with 3 x 250 ml of methylene chloride. The methylene chloride solution was washed with 250 ml water. The organic phase was separated, dried over sodium sulfate and concentrated in vacuo.

A portion of the crude ester (530 mg) was dissolved in 50 ml of methanol. The solution was stirred in a pressure bottle and saturated with ammonia at 0°C. The bottle was sealed and the solution was stirred at room temperature for 48 hours. The solution was concentrated in vacuo. This gave a solid which was purified by flash chromatogrphy in a 97:3 chloroform/methanol solvent system to 245 mg of purified product.
HPLC: 99% pure.
MS: M^+ (14 ev) m/e 440
NMR: Consistent with title structure.

Anal. calc'd for $C_{26}H_{21}FN_4O_2 \cdot 0.53H_2O$
N, 12.45; C, 69.39; H, 4.82;
Found: N, 12.27; C, 69.32; H, 4.80.

EXAMPLE 124

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-(2-indolylmethylamino)-2H-1,4-benzodiazepin-2-one

3-(RS)-Chloro-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (150 mg, 0.520 mmol) and 2-aminomethylindole (75.9 mg, 0.520 mmol) were combined in 1,2-dimethoxyethane (3 ml) and the mixture stirred 20 min. at 25°C. The mixture was evaporated to dryness in vacuo and the residue treated with H_2O and extracted with EtOAc (3x). The combined extracts were washed with H_2O (1X), dried over $MgSO_4$, filtered and stripped to dryness in vacuo to give an orange oil which, after chromatography on silica gel (4% MeOH in CH_2Cl_2) provided the title compound as a white solid from ether: (m.p. 200-202°).
TLC: Silica GF (5% MeOH in CH_2Cl_2), R_f = 0.37, single homogeneous component.
NMR: Consistent with title structure.
HPLC: Greater than 97.7% pure.
MS: Molecular ion at m/e=398.
Anal. calc'd for $C_{24}H_{19}FN_4O$:
C, 72.35; H, 4.81; N, 14.06;
Found: C, 72.48; H, 4.81; N, 13.69.

EXAMPLE 125

1,3-Dihydro-3-(RS)-(phenylaminomethylcarbonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-3-(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (100 mg, 0.37 mmol) and N-phenyl glycine (64 mg, 0.42 mmol) were combined at room temperature in 5 ml of methlylene chloride. To this reaction mixture was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (81 mg, 0.42 mmole). The pH of the reaction mixture was then adjusted to 8.5 with triethylamine and stirring was continued at room temperature overnight. More N-phenylglycine and carbodiimide reagent were added (0.2 equivalents) and stirring was continued. The reaction mixture was partitioned between methylene chloride and 10% citric acid solution after 48 hours reaction time. The phases were separated and the organic layer was washed in succession with 20% citric acid solution (1 x 30 ml), saturated sodium bicarbonate solution (2 x 30 ml) and brine. The dried ($MgSO_4$) extracts were concentrated to yield 200 mg of crude product. Preparative thick layer chromatography (chloroform - ethanol - ammonia 92:8:0.8 v/v) afforded the analytical sample (100 mg), m.p. 145-146°.

NMR ($CDCl_3$): Consistent with the title structure.

MS (14 ev): 402 (M^+), 265.

Anal. calc'd for $C_{23}H_{19}FN_4O_2 \cdot 0.55\ CHCl_3$

N, 11.97; C, 60.43; H, 4.21;

Found: N, 11.80; C, 60.37; H, 4.06.

EXAMPLE 126

1,3-Dihydro-3-(RS)-(5-methoxyindole-2-carbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

3-(RS)-Amino-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (50 mg, 0.186 mmol) was suspended in 1 ml of methylene chloride. 5-Methoxyindole-2-carboxylic acid (36.9 mg, 0.207 mmol) was added to the suspension followed by the addition of 38.5 mg (0.2 mmol) of EDC. The mixture was brought to pH ~ 8 with ~ 60 µl of triethylamine. The solid which formed after 3 min. was filtered after 5 hours and washed with chloroform. The filtrate was applied to a 2000 µ preparative TLC plate and eluted with 90:10:1 chloroform:methanol:water (CMW). The product was extracted from silica with methanol and evaporated.

HPLC: 98% pure.

MS: M^+ (14 ev) m/e 442

NMR: Consistent with title structure.

Anal. calc'd for $C_{25}H_{19}FN_4O_3 \cdot 0.1CHCl_3$

N, 12.33; C, 66.34; H, 4.24;

Found: N, 10.59; C, 66.19; H, 4.23.

EXAMPLE 127

1,3-Dihydro-3-(RS)-(1-methylindole-2-carbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one

3-(RS)-Amino-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (50 mg, 0.186 mmol) was suspended in 1 ml of methylene chloride. 1-Methylindole-2-carboxylic acid (36.2 mg, 0.2 mmol) was added to the solution followed by the addition of 38.5 mg (0.2 mmol) of EDC. The pH of the solution was brought to ~8 with ~60 µl of triethylamine.

After stirring for 4 hours the product was purified by preparative TLC on a 2000 μ silica gel plate with a 95:5:0.5 chloroform/methanol/water solvent system. The product band was collected and isolated by washing the silica with 90:10:1 CMW. yield 16.5 mg.
HPLC: 99% pure
MS: M^+ (14 ev) m/e 426
NMR: Consistent with title structure.
Analysis calc'd for $C_{25}H_{19}FN_4O_2 \cdot 0.8CH_3OH$
N, 12.39; C, 68.54; H, 4.95;
Found: N, 12.34; C, 68.29; H, 4.18.

EXAMPLE 128

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-(2-benzofurancarbonylamino)-2H-1,4-benzodiazepin-2-one

3-(RS)-Amino-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (80 mg, 0.297 mmol), benzofuran-2-carboxylic acid (48 mg, 0.297 mmol), and EDC (56.9 mg, 0.297 mmol) were combined in CH_2Cl_2 (3 ml) and the pH adjusted to 9.5 with triethylamine (41 μl, 0.297 mmol). After stirring 30 minutes at 25°C, the reaction was concentrated and chromatographed on silica gel (3% MeOH in CH_2Cl_2) to give the title compound as a white solid from CH_2Cl_2/Et_2O: (m.p. 289-291°).
TLC: Silica GF (5% MeOH in CH_2Cl_2), R_f=0.48, single homogeneous component.
NMR: Consistent with title structure and verified the presence of 0.15 CH_2Cl_2 and 0.1 $(C_2H_5)_2O$.
HPLC: Greater than 99.7% pure.
M.S.: Mol. ion = 413 m/e (free base).
Anal. Calc'd for $C_{25}H_{16}FN_3O_3 \cdot 0.15\ CH_2Cl_2 \cdot 0.10\ (C_2H_5)_2O$:
Calc'd: C, 68.01; H, 4.02; N, 9.69;
Found: C, 68.22; H, 3.86; N, 9.36.

EXAMPLE 129

1-Ethoxycarbonylmethyl-1,3-dihydro-3(RS)-(4-chlorophenylcarbonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

To a suspension of sodium hydride (50%) (24.4 mg, 0.51 mmole) in 2 ml of dry dimethylformamide at 0°C was added, under nitrogen, 1,3-dihydro-3(RS)-(4-chlorophenylcarbonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (197.3 mg, 0.48 mmole). The resulting reaction mixture became homogeneous over a one-hour period, was stirred one hour more at 0°C and then treated with ethylbromoacetate (55 µl, 0.50 mmole). The reaction mixture was warmed to room temperature and after one hour was quenched with brine. The aqueous mixture was extracted with ethyl acetate and the combined organic extracts were washed with brine. Rotoevaporation of the dried extracts ($MgSO_4$) gave a semi-solid which was chromatographed on silica gel (chloroform-methanol-ammonia 95:5:0.5 v/v elution) to afford 64 mg of the analytical sample. mp 172° (soften), 177-178°C.

NMR ($CDCl_3$): Consistent with the title structure.

MS (14 ev): 493 (M^+), 364, 354, 338, 327, 313

Analysis calc'd for $C_{26}H_{21}ClFN_3O_4 . 0.1\ C_4H_8O_2$

N, 8.35; C, 63.05; H, 4.32;

Found: N, 8.16; C, 62.89; H, 4.44.

EXAMPLE 130

1,3-Dihydro-3-(RS)-(4-chlorophenylcarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-3-(RS)-amino-5-phenyl-2H-1,4-benzodiazepin-2-one (500 mg, 1.98 mmole) and p-chlorobenzoyl chloride (255 µl, 2.00 mmole) were

combined at room temperature in 30 ml of methylene chloride. The resulting solution was protected from moisture and stirred at room temperature overnight. The reaction mixture was diluted with 70 ml of methylene chloride and washed with sodium bicarbonate solution (sat.) and brine. The organic extracts were dried ($MgSO_4$) and concentrated to give the crude product. Trituration with ether afforded the analytical sample as a white solid.

NMR ($CDCl_3$): Consistent with the title structure.
MS (14 ev): 389 (M^+), 250, 234.
Analysis calc'd for: $C_{22}H_{16}ClN_3O_2$
N, 10.78; C, 67.78; H, 4.13;
Found: N, 10.71; C, 67.79; H, 3.97.

EXAMPLE 131

1,3-Dihydro-1-methyl-3-(RS)-(4-chlorophenylcarbonyl)-amino-5-phenyl-2H-1,4-benzodiazepin-2-one

To a suspension of sodium hydride (50%) (10 mg, 0.21 mmole) in 1 ml of dry dimethylformamide at 0°C was added, under a nitrogen, 1,3-dihydro-3-(RS)-(4-chlorophenylcarbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one (65.5 mg, 0.166 mmole). The resulting reaction mixture became homogeneous over a one-hour period, was stirred one hour more at 0°C and then treated with iodomethane (10.8 µl, 0.17 mmole). The reaction mixture was warmed to room temperature and after one hour was quenched with brine. The aqueous mixture was extracted with ethyl acetate and the combined organic extracts were washed with brine. Rotoevaporation of the dried extracts ($MgSO_4$) gave a semi-solid which was chromatographed on silica gel (chloroform-methanol-ammonia 95:5:0.5 v/v elution) to give the analytical sample.

NMR ($CDCl_3$): Consistent with the title structure;
MS (14 ev): 403 (M^+)
Analysis calc'd for: $C_{23}H_{18}ClN_3O_2$:
N, 10.40; C, 68.40; H, 4.49;
Found: N, 10.11; C, 68.50; H, 4.57.

EXAMPLE 132

1-Carboxymethyl-1,3-dihydro-3-(RS)-(4-chlorophenylcarbonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

To a suspension of sodium hydride (50%) (14.0 mg, 0.30 mmole) in 2 ml of dry dimethylformamide at 0°C was added, under nitrogen, 1,3-dihydro-3-(RS)-(4-chlorophenylcarbonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (103.0 mg, 0.25 mmole). The resulting reaction mixture became homogeneous over a one-hour period, was stirred one hour more at 0°C and then treated with 1 ml of dimethylformamide containing sodium iodoacetate (56 mg) (0.27 mmole). The reaction mixture was warmed to room temperature and after 12 hours was quenched with brine. The aqueous mixture was extracted with ethyl acetate and the combined organic extracts were washed with brine. Rotoevaporation of the dried extracts ($MgSO_4$) gave a semi-solid which was chromatographed on silica gel (chloroform-methanol-acetic acid, 93:6:1 v/v) to provide the analytical sample: (m.p. 225-228°C, from methanol).
FABMS: m/e = 466 (M + H), 245, 177.
NMR (DMSO-d_6): consistent with title structure.
Anal. Calc'd for $C_{24}H_{17}ClFN_3O_4$ 0.45NaI 0.75 H_2O
C, 52.71; H, 3.41; N, 7.68.
Found: C, 52.87; H, 3.64; N, 7.43.

EXAMPLE 133

1,3-Dihydro-3-(RS)-(2-indolinecarbonylamino)-5-phenyl-2 H-1,4-benzodiazepin-2-one

3-(RS)-Amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (100 mg, 0.398 mmol), l-indoline-2-carboxylic acid (64.9 mg, 0.398 mmol), 1-hydroxybenzotriazole hydrate (HBT, 53.8 mg, 0.398 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC, 76.3 mg, 0.398 mmol) were combined in DMF (2 ml) and the pH of the solution was adjusted to 9.0-9.5 with triethylamine (TEA, 95 µl, 0.683 mmol). After stirring 15 minutes at 25°C, the DMF was removed in vacuo, the residue treated with H_2O and extracted with EtOAc (3x). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and stripped to dryness in vacuo to give a white solid (180 mg). Flash chromatography on silica gel (267/10/1 of CH_2Cl_2/MeOH/concentrated NH_4OH) gave a white solid (38 mg) from EtOAc/hexane. The product is a single stereoisomer whose absolute configuration is unknown; m.p. 252-272°C (slowly shrinkes to a cloudy melt).

TLC: Silica GF (190/10/1 of CH_2Cl_2/MeOH/concentrated NH_4OH), R_f=0.40, single, clean component.

NMR: Consistent with title structure and verifies the presence of EtOAc.

HPLC: Greater than >96% pure.

MS: Molecular ion at m/e=396.

Anal. calc'd for $C_{24}H_{20}N_4O_2 \cdot 0.45C_4H_8O_2$

C, 71.06; H, 5.46; N, 12.85;

Found: C, 70.71; H, 5.11; N, 13.20.

EXAMPLE 134

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-(p-trifluoromethylbenzoylamino)-2H-1,4-benzodiazepin-2-one

1,3-Dihydro-3-(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one (42 mg, 0.156 mmole) and p-trifluoromethylbenzoyl chloride (32.5 mg, 0.156 mmole) were combined in 3 ml of methylene chloride (CH_2Cl_2), treated with triethylamine (0.0157 g, 0.156 mmole) and stirred at room temperature 15 minutes. The mixture was diluted with CH_2Cl_2 (20 ml), washed with 10% citric acid (2 x 5 ml), dilute sodium bicarbonate (2 x 5 ml), and water (2 x 5 ml), dried over sodium sulfate, filtered, and evaporated to dryness in vacuo. The residue was crystallized from ethyl acetate (0.4 ml)/ether (1 ml) to give the title compound which was dried in vacuo at 90°: (m.p. 209-211°).

TLC: Single spot, R_f=0.62, silica gel plate, 90:10:1:1 (v:v:v:v) CH_2Cl_2:MeOH:HOAc:H_2O.

NMR: The spectrum was consistent with the title structure and verified the presence of EtOAc.

HPLC: Greater than 98% pure.

MS: Molecular ion at m/e=441.

Anal. calc'd for $C_{23}H_{15}F_4N_3O_2 \cdot 0.2EtOAc$:

C, 62.27; H, 3.64; N, 9.16;

Found: C, 62.25; H, 3.61; N, 9.11.

EXAMPLE 135

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-(p-methylbenzoylamino)-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using p-methylbenzoyl chloride (24 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The

title compound was crystallized from CH_2Cl_2 (3 ml)/Et_2O (1 ml) and dried in vacuo at 90°: (m.p. 275-276° (d)).

TLC: Single spot, R_f=0.62, silica gel plate, 90:10:1:1 (v:v:v:v) CH_2Cl_2:MeOH:HOAc:H_2O.

NMR: The spectrum was consistent with the title structure.

HPLC: Greater than 98% pure.

MS: Molecular ion at m/e=387.

Anal. calc'd for $C_{23}H_{18}FN_3O_2 \cdot 0.4H_2O$:
C, 70.00; H, 4.80; N, 10.65;
Found: C, 70.04; H, 4.68; N, 10.56.

EXAMPLE 136

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-(p-methoxybenzoylamino)-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using p-methoxybenzoyl chloride (26.6 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The title compound was crystallized from CH_2Cl_2 (2 ml)/Et_2O (1 ml) and dried in vacuo at 90°: (m.p. 231-233°).

TLC: Single spot, R_f=0.47, silica gel plate, 5% (v/v) MeOH/CH_2Cl_2.

NMR: The spectrum was consistent with the title structure.

HPLC: Greater than 97% pure.

MS: Molecular ion at m/e=403.

Anal. calc'd for $C_{23}H_{18}FN_3O_3$:
C, 68.48; H, 4.50; N, 10.42;
Found: C, 68.62; H, 4.60; N, 10.36.

EXAMPLE 137

3-(RS)-(o-Chlorobenzoylamino)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

3-(RS)-Amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one (250 mg, 0.93 mmol) was suspended in methylene chloride (10 ml) and treated with o-chlorobenzoylchloride (0.124 ml, 0.97 mmol) followed by triethylamine (0.143 ml, 0.97 mmol). The solution was stirred at room temperature overnight. The reaction solution was chromatographed on silica gel (chloroform followed by 97/3 chloroform/methanol) and the combined product fractions were evaporated to dryness in vacuo. TLC: Silica gel (90:10:1, $CHCl_3$:CH_3OH:H_2O), R_f=0.85.
NMR: Consistent with structure.
HPLC: 99% pure.
MS: Molecular ion at m/e=389.
Anal. calc'd for $C_{22}H_{16}ClN_3O_2$:
C, 67.78; H, 4.14; N, 10.77;
Found: C, 67.34; H, 4.00; N, 10.72.

EXAMPLE 138

3-(RS)-(o-Chlorobenzoylmethylamino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

3-(RS)-1,3-Dihydro-(o-Chlorobenzoylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one (200 mg, 0.51 mmol) and sodium hydride (52 mg of a 50% suspension in mineral oil, 1.094 mmol) were stirred in 2 ml of dry, degassed dimethylformamide under nitrogen in an ice bath. The mixture was stirred until homogeneous. After 2 hours, methyl iodide (38 µl, 1.094 mmol) was added in one portion. The reaction was stirred for 1 hour at 0°C and 1 hour at room temperature. The

reaction was quenched with 3 ml of saturated sodium chloride solution. The mixture was extracted with ethyl acetate. The clear solution obtained when chloroform was added was evaporated to dryness then chromatographed on silica gel with chloroform as the elution solvent. The 7:1 mixture of the di and mono substituted compounds was further purified by preparative TLC. (Analtech silica gel 2000 μ prep TLC plates developed twice in a 98:2 chloroform/ methanol solvent system).

TLC: Silica gel 97:2 $CHCl_3$:MeOH, R_f=0.35.

NMR: Consistent with structure.

MS: Molecular ion m/e=417

HPLC: 98%.

Anal. calc'd for $C_{24}H_{20}ClN_3O_2$ 0.35$CHCl_3$:
C, 63.62; H, 4.46; N, 9.14;
Found: C, 63.40; H, 4.55; N, 8.97.

EXAMPLE 139

3-(RS)-(o-Chlorobenzoylamino)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

3-(RS)-1,3-Dihydro-(o-Chlorobenzoylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one (207 mg, 0.53 mmol) and sodium hydride (26 mg of a 50% suspension in mineral oil, 0.54 mmol) were stirred in 2 ml of dry, degassed dimethylformamide under nitrogen in an ice bath. The mixture was stirred until homogenous. After 2 hours, methyl iodide (34 μl, 0.547 mmol) was added in one portion. (The remainder of the experiment proceeds as described in Example 139).

NMR: Consistent with structure.

HPLC: 98%.

MS: Molecular ion m/e 403.

Anal. calc'd for $C_{23}H_{18}ClN_3O_2$ $0.62H_2O$

C, 66.56; H, 4.67; N, 10.12;

Found: C, 66.71; H, 4.53; N, 9.90.

EXAMPLE 140

3-(RS)-(m-Chlorobenzoylamino)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 137 was carried out using m-chlorobenzoyl chloride in place of o-chlorobenzoylchloride. The reaction was chromatographed using chloroform as the elution solvent.

TLC: Silica gel 90:10:1 CMA; R_f=0.8.

NMR: Consistent with structure.

HPLC: 96%.

MS: Molecular ion at m/e 389.

Anal. calc'd for $C_{22}H_{16}N_3O_2$ $0.62CHCl_3$:

C, 59.86; H, 3.69; N, 9.30;

Found: C, 59.99; H, 3.75; N, 9.18.

EXAMPLE 141

3-(RS)-(3,4-Dichlorobenzoylamino)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

The EDC procedure in Example 126 was carried out using 3,4-dichlorobenzoic acid in place of 5-methoxy-indole-2-carboxylic acid. The reaction product was dissolved in chloroform and chromatographed with chloroform followed by 99:1 $CHCl_3$:MeOH(CM).

TLC: Silica gel 97:3 CM, R_f=0.45.

HPLC: 100%.

NMR: Consistent with structure.

MS: Molecular ion at m/e 423.

Anal. calc'd for $C_{22}H_{15}Cl_2N_3O_2$ 0.08$CHCl_3$
C, 61.12; H, 3.50; N, 9.69;
Found: C, 61.05; H, 3.50; N, 9.30.

EXAMPLE 142

3-(RS)-(p-Chlorobenzoylamino)1,3-dihydro-5-(2'-fluorophenyl)-1-methyl-4-oxo-2H-1,4-benzodiazepin-2-one

3-(RS)-(p-Chlorobenzoylamino)1,3-Dihydro-5-(2'-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one (50 mg, 0.118 mmol) was stirred in 3 ml of chloroform. m-Chloroperoxybenzoic acid (23.6 mg, 0.137 mmol) was added. After stirring overnight another 23.6 mg of MCPBA was added. The solution was stirred for 48 hours then diluted with chloroform and washed with cold saturated sodium bicarbonate. The chloroform solution was dried over sodium sulfate and evaporated. The residue obtained after evaporation was purified by preparative TLC with 98:2 $CHCl_3$:MeOH (CM) as the developing solvent.

TLC: Silica gel 98:2 CM, R_f=0.4 CM.
NMR: Consistent with structure.
HPLC: 95%.
MS: Molecular ion at m/e=437.
Anal. calc'd for $C_{23}H_{17}ClFN_3O_3$ 0.05$CHCl_3$:
C, 62.37; H, 3.87; N, 9.46;
Found: C, 62.41; H, 3.80; H, 9.43.

EXAMPLE 143

1,3-Dihydro-5-Phenyl-3-(RS)-(4'-methylthiobenzoylamino)-2H-1,4-benzodiazepin-2-one

The EDC procedure in Example 126 was carried out using 4-methyl thiobenzoic acid in place of 5-methoxyindole-2-carboxylic acid. The reaction

solution was chromatographed on a silica gel column with chloroform followed by 99:1 $CHCl_3$:MeOH (CM).
TLC: Silica gel 97:3 CM, R_f=0.3
NMR: Consistent with structure.
HPLC: 97%.
MS: Molecular ion at m/e 401.
Anal. calc'd for $C_{23}H_{19}N_3O_2S$ 0.65$CHCl_3$:
C, 59.28; H, 4.13; N, 8.77;
Found: C, 59.33; H, 4.21; N, 8.57.

EXAMPLE 144

1-3-Dihydro-3-(RS)-(4'-Fluorobenzoylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 137 was carried out using 4-fluorobenzoyl chloride in place of o-chlorobenzoyl chloride. The reaction was chromatographed on silica gel using chloroform as the elution solvent.
TLC: Silica gel 97:3 $CHCl_3$:MeOH (CM), R_f=0.33.
NMR: Consistent with structure.
HPLC: 95%.
MS: Molecular ion at m/e 373.
Anal. calc'd for $C_{22}H_{16}FN_3O_2$ 0.2H_2O:
C, 70.09; H, 4.39; N, 11.15;
Found: C, 70.14; H, 4.36; N, 10.93.

EXAMPLE 145

1,3-Dihydro-5-Phenyl-3-(RS)-(4'-trifluoromethyl-benzoylamino)-2H-1,4-benzodiazepin-2-one

The procedure of Example 137 was carried out using 4-trifluoromethylbenzoyl chloride in place of o-chlorobenzoyl chloride. The reaction was chromatographed on silica gel using chloroform as the elution solvent.

TLC: Silica gel 97:3 $CHCl_3$:MeOH (CM), R_f=0.3.
NMR: Consistent with structure.
HPLC: 99%.
MS: Molecular ion at m/e 423.
Anal. calc'd for $C_{23}H_{16}F_3N_3O_2$:
C, 65.24; H, 3.81; N, 9.92;
Found: C, 65.14; H, 3.94; N, 9.69.

EXAMPLE 146

1,3-Dihydro-3-(RS)-(4'-tert-Butylbenzoylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 137 was carried out using 4-tert-butylbenzoyl chloride in place of o-chlorobenzoyl chloride. The reaction was chromatographed on silica gel using chloroform as the elution solvent.
TLC: Silica 97:3, $CHCl_3$:MeOH, R_f=0.35.
NMR: Consistent with structure.
HPLC: 98%.
MS: Molecular ion at m/e 411.
Anal. calc'd for $C_{26}H_{25}N_3O_2$ 0.14$CHCl_3$:
C, 73.31; H, 5.92; N, 9.81;
Found: C, 73.69; H, 6.07; N, 9.78.

EXAMPLE 147

3-(RS)-(3,5-Dichlorobenzoylamino)1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

The EDC procedure in Example 126 was carried out using 3,5-dichlorobenzoic acid in place of 5-methoxyindole-2-carboxylic acid. The reaction was diluted with chloroform and chromatographed on a silica gel column with chloroform as the elution solvent.

TLC: Silica gel 97:3 $CHCl_3$:MeOH (CM), R_f=0.5
NMR: Consistent with structure.
HPLC: 96%.
MS: Molecular ion at m/e 423.
Anal. calc'd for $C_{22}H_{15}Cl_2N_3O_2$:
C, 62.27; H, 3.56; N, 9.90;
Found: C, 62.65; H, 3.67; N, 9.80.

EXAMPLE 148

1-3-Dihydro-3-(RS)-(p-Hydroxybenzoylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one

The EDC procedure in Example 126 was carried out using p-hydroxybenzoic acid in place of 5-methoxy-indole-2-carboxylic acid. The reaction was chromatographed on silica gel with chloroform as the elution solvent.
TLC: Silica gel 97:3 $CHCl_3$:MeOH, R_f=0.50.
NMR: Consistent with structure.
HPLC: 99%.
MS: Molecular ion at 371.
Anal. calc'd for $C_{22}H_{17}N_3O_3$:
C, 71.15; H, 4.61; N, 11.31;
Found: C, 70.05; H, 4.63; H, 11.21.

EXAMPLE 149

3-(RS)-(4'-Cyanobenzoylamino)1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure in Example 137 was carried out using 4-cyanobenzoyl chloride in place of o-chloro-benzoyl chloride. The reaction was chromatographed on silica gel using chloroform followed by 98:2 $CHCl_3$:MeOH (CM) as the elution solvents.
TLC: Silica gel 97:3 CM, R_f=0.3.

NMR: Consistent with structure.
HPLC: 99.6%.
MS: Molecular ion at m/e=380.
Anal. calc'd for $C_{23}H_{16}N_4O_2$ $0.41H_2O$
C, 71.24; H, 4.37; N, 14.45;
Found: C, 71.53; H, 4.37; N, 14.73.

EXAMPLE 150

3(S)-(-)-3-(2-Chlorobenzoylamino)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(S)-(-)-3-amino-1,3-dihydro-5-phenyl-1-methyl-2H-1,4-benzodiazepin-2-one (41.4 mg, 0.156 mmole) in place of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one and 2-chlorobenzoyl-chloride (27.3 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The product was chromatographed on silica gel (5% (v/v) Et_2O in CH_2Cl_2 elution). The combined product fractions were evaporated to dryness in vacuo to give the title compound which was dried in vacuo at 78°C: (m.p. 100-118°C).
TLC: Single spot, R_f=0.24, silica gel plate, 5% (v/v) Et_2O in CH_2Cl_2.
NMR: Consistent with structure.
HPLC: Greater than 99% pure.
MS: Molecular ion at m/e=403.
$[\alpha]_D^{25}$ = -90.4° (1.15 mg/ml, CH_2Cl_2).
Anal. calc'd for $C_{23}H_{18}ClN_3O$:
C, 68.40; H, 4.49; N, 10.41;
Found: C, 68.20; H, 4.73; N, 10.07.

EXAMPLE 151

3(R)-(+)-3-(2-Chlorobenzoylamino)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(R)-(+)-3-amino-1,3-dihydro-5-phenyl-1-methyl-2H-1,4-benzodiazepin-2-one (41.4 mg, 0.156 mmole) in place of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one, and 2-chlorobenzoyl chloride (27.3 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The product was chromatographed on silica gel (5% (v/v) Et_2O in CH_2Cl_2 elution). The combined product fractions were evaporated to dryness in vacuo to give the title compound which was dried in vacuo at 78°C: (m.p. 102-120°C).

TLC: Single spot, R_f=0.24, silica gel plate, 5% (v/v) Et_2O in CH_2Cl_2.

NMR: Consistent with structure.

HPLC: Greater than 98% pure.

MS: Molecular ion at m/e=403.

$[\alpha]_D^{25}$ = +95.4° (1.75 mg/ml, CH_2Cl_2).

Anal. calc'd for $C_{23}H_{18}ClN_3O$:

C, 68.40; H, 4.49; N, 10.41;

Found: C, 68.74; H, 4.68; N, 10.16.

EXAMPLE 152

1,3-Dihydro-3(RS)-(p-dimethylaminobenzoylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using p-dimethylaminobenzoyl chloride (28.6 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The citric acid and sodium bicarbonate washes were omitted. The title compound was

crystallized from CH_2Cl_2 (6 ml)/Et_2O (5 ml) and dried in vacuo at 90°: (m.p. 256-258°C).
TLC: Single spot, R_f=0.60, silica gel plate, 90:10:1:1 (v/v/v/v) CH_2Cl_2:MeOH:HOAc:H_2O.
NMR: The spectrum was consistent with the title structure and verified the presence of H_2O.
HPLC: Greater than 98% pure.
MS: Molecular ion at m/e=416.
Anal. calc'd for $C_{24}H_{21}FN_4O_2 \cdot 0.15H_2O$:
C, 68.77; H, 5.12; N, 13.37;
Found: C, 68.73; H, 5.16; N, 13.27.

EXAMPLE 153

1,3-Dihydro-3(RS)-(3,4-dimethoxybenzoylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3,4-dimethoxybenzoyl chloride (31.3 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The title compound was crystallized from CH_2Cl_2 (1.5 ml)/Et_2O (3 ml) and dried in vacuo at 90°: (m.p. 206-207.5°C).
TLC: Single spot, R_f=0.64, silica gel plate, 90:10:1:1 (v:v:v:v) CH_2Cl_2:MeOH:HOAc:H_2O.
NMR: The spectrum was consistent with the title structure and verified the presence of Et_2O and CH_2Cl_2.
HPLC: Greater than 99% pure.
MS: Molecular ion at m/e=433.
Anal. calc'd for $C_{24}H_{20}FN_3O_4 \cdot 0.13C_4H_{10}O \cdot 0.13CH_2Cl_2$:
C, 65.24; H, 4.79; N, 9.26;
Found: C, 65.22; H, 4.55; N, 9.14.

EXAMPLE 154

3(S)-(+)-3-(3-Bromobenzoylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(S)-(-)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one (44.2 mg, 0.156 mmole) in place of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one and 3-bromobenzoyl chloride (34.2 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The title compound was crystallized from Et_2O and dried in vacuo at 100°C: (m.p. 172-178°C).

TLC: Single spot, R_f=0.66, silica gel plate, 15% (v/v) Et_2O in CH_2Cl_2.

NMR: Consistent with structure.

HPLC: Greater than 99% pure.

MS: Molecular ion at m/e=465.

$[\alpha]_D^{25}$ = +16.7° (0.0025 g/ml, CH_2Cl_2).

Anal. calc'd for $C_{23}H_{17}BrFN_3O_2$:

C, 59.24; H, 3.67; N, 9.01;

Found: C, 59.45; H, 3.80; N, 8.97.

EXAMPLE 155

1,3-Dihydro-5-phenyl-3(RS)-(3-trifluoromethylthiobenzoylamino)-2H-1,4-benzodiazepin-2-one

3(RS)-Amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (80.0 mg, 0.318 mmole), 3-trifluoromethylthiobenzoic acid (70.7 mg, 0.318 mmole), HBT (43.0 mg, 0.318 mmole) and EDC (61.0 mg, 0.318 mmole) were combined in dry DMF (2 ml) and stirred at room temperature. The pH of the mixture was adjusted to 9.0-9.5 with triethylamine (64.4 mg, 0.636 mmole) and the mixture stirred for 10 minutes.

The DMF was removed in vacuo, and the residue was treated with 10% citric acid and extracted with EtOAc. The combined organic fractions were washed with sodium carbonate solution, dried over Na_2SO_4, filtered, and evaporated to dryness in vacuo. The residue was crystallized from EtOAc to give the title compound which was dried in vacuo at 100°C: (m.p. 230-232°C).

TLC: Single spot, R_f=0.32, silica gel plate, 15% (v/v) Et_2O in CH_2Cl_2.

NMR: Consistent with structure.

HPLC: Greater than 98% pure.

MS: Molecular ion at m/e=455.

Anal. calc'd for $C_{23}H_{16}F_3N_3O_2S$:

C, 60.65; H, 3.54; N, 9.23;

Found: C, 60.82; H, 3.51; N, 9.35.

EXAMPLE 156

3(S)-(+)-3-(4-Bromobenzoylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(S)-(-)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one (44.2 mg, 0.156 mmole) in place of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one and 4-bromobenzoyl chloride (34.2 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The title compound was chromatographed on silica gel (5% Et_2O in CH_2Cl_2 elution) and the product fractions evaporated to dryness in vacuo. The title compound was dried in vacuo at 82°C: (m.p. 123-135°C).

TLC: Single spot, R_f=0.46, silica gel plate, 10% (v/v) Et_2O in CH_2Cl_2.
NMR: Consistent with structure.
HPLC: Greater than 99% pure.
MS: Molecular ion at m/e=465.
$[\alpha]_D^{25}$ = +9.6° (0.0023 g/ml, CH_2Cl_2).
Anal. calc'd for $C_{23}H_{17}BrFN_3O_2$:
C, 59.24; H, 3.67; N, 9.01;
Found: C, 59.12; H, 3.75; N, 8.77.

EXAMPLE 157

3(S)-(+)-3-(4-t-Butylbenzoylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(S)-(-)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one (44.2 mg, 0.156 mmole) in place of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one and 4-t-butylbenzoyl chloride (30.7 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The product was chromatographed on silica gel (4% Et_2O in CH_2Cl_2 elution), and the product fractions evaporated to dryness in vacuo. The title compound was dried in vacuo at 82°C: (m.p. 184-190°C).
TLC: Single spot, R_f=0.37, silica gel plate, 5% (v/v Et_2O in CH_2Cl_2).
NMR: Consistent with structure.
HPLC: Greater than 99% pure.
MS: Molecular ion at m/e=443.
$[\alpha]_D^{25}$ = +6.7° (0.0021 g/ml, CH_2Cl_2).
Anal. calc'd for $C_{27}H_{26}FN_3O_2$:
C, 73.12; H, 5.91; N, 9.48;
Found: C, 73.03; H, 6.11; N, 9.44.

EXAMPLE 158

1,3-Dihydro-5-(2-fluorophenyl)-3(RS)-(pyrrole-2-carbonylamino)-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using pyrrole-2-carbonyl chloride (20.2 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. Without washing, the reaction mixture was chromatographed on silica gel (225:10:1:1 (v:v:v:v) CH_2Cl_2:MeOH:HOAc:H_2O elution). The combined product fractions were evaporated to dryness *in vacuo* and crystallized from EtOAc to give the title compound which was dried *in vacuo* at 82°C: (m.p. 271-274°C).
TLC: Single spot, R_f=0.35, silica gel plate, 180:10:1:1 (v/v/v/v) CH_2Cl_2:MeOH:HOAc:H_2O.
NMR: Consistent with structure, verifies presence of 0.25 EtOAc.
HPLC: Greater than 95% pure.
MS: Molecular ion at m/e=362.
Anal. calc'd for $C_{20}H_{15}FN_4O_2 \cdot 0.25C_4H_{10}O$:
C, 65.62; H, 4.46; N, 14.58;
Found: C, 65.60; H, 4.55; N, 14.53.

EXAMPLE 159

3(S)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(4-iodobenzoylamino)-1-methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(S)-(-)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one (44.2 mg, 0.156 mmole) in place of 1,3-(dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one and 4-iodobenzoyl chloride (41.6 mg, 0.156 mmole in place of p-trifluoromethylbenzoyl chloride. The product was chromatographed on silica gel (5% (v/v) Et_2O in

CH_2Cl_2 elution) and the product fractions evaporated to dryness in vacuo. The title compound was dried in vacuo at 82°C: (m.p. 128-140°C).
TLC: Single spot, R_f=0.51, silica gel plate, 10% (v/v) Et_2O in CH_2Cl_2.
NMR: Consistent with structure.
HPLC: Greater than 99% pure.
MS: Molecular ion at m/e=513.
$[\alpha]_D^{25}$ = +8.4° (0.0028 g/ml, CH_2Cl_2).
Anal. calc'd for $C_{23}H_{17}FIN_3O_2$:
C, 53.82; H, 3.34; N, 8.19;
Found: C, 53.72; H, 3.44; N, 8.00.

EXAMPLE 160

1,3-Dihydro-3(RS)-(2-naphthoylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(RS)-amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (39.2 mg, 0.156 mmole) in place of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one and 2-naphthoyl chloride (29.7 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The product was chromatographed on silica gel (15% (v/v) Et_2O in CH_2Cl_2 elution). The combined product fractions were evaporated to dryness in vacuo and crystallized from CH_2Cl_2/EtOAc to give the title compound which was dried in vacuo at 82°C: (m.p. 293-294°C).
TLC: Single spot, R_f=0.28, silica gel plate, 15% (v/v) Et_2O in CH_2Cl_2.
NMR: Consistent with structure.
HPLC: Greater than 99% pure.
MS: Molecular ion at m/e=405.

Anal. calc'd for $C_{26}H_{19}N_3O_2$:
C, 77.02; H, 4.72; N, 10.37;
Found: C, 76.88; H, 4.85; N, 10.50.

EXAMPLE 161

3(S)-(-)-3-(2-Bromobenzoylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(S)-(-)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one (44.2 mg, 0.156 mmole) in place of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one and 2-bromobenzoyl chloride (34.2 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The product was chromatographed on silica gel (5% (v/v) Et_2O in CH_2Cl_2 elution). The combined product fractions were evaporated to dryness. The residue was crystallized from Et_2O to give the title compound which was dried in vacuo at 82°C: (m.p. 165-185°C).

TLC: Single spot, R_f=0.38, silica gel plate, 10% (v/v) Et_2O in CH_2Cl_2.

NMR: Consistent with structure.

HPLC: Greater than 99% pure.

MS: Molecular ion at m/e=465.

$[\alpha]_D^{25}$ = -24.1° (0.0037 g/ml, CH_2Cl_2).

Anal. calc'd for $C_{23}H_{17}BrFN_3O_2$:
C, 59.24; H, 3.67; N, 9.01;
Found: C, 59.14; H, 3.61; N, 9.06.

EXAMPLE 162

3(S)-(+)-3-(4-Cyanobenzoylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(S)-(-)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one (44.2 mg, 0.156 mmole) in place of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one and 4-cyanobenzoyl chloride (25.8 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The product was chromatographed on silica gel (8% (v/v) Et_2O in CH_2Cl_2 elution). The combined product fractions were evaporated to dryness in vacuo to give the title compound which was dried in vacuo at 82°C: (m.p. 130-147°C).

TLC: Single spot, R_f=0.29, silica gel plate, 10% (v/v) Et_2O in CH_2Cl_2.

NMR: Consistent with structure, verifies presence of 0.1 Et_2O.

HPLC: Greater than 98% pure.

MS: Molecular ion at m/e=412.

$[\alpha]_D^{25}$ = +13.0° (0.0027 g/ml, CH_2Cl_2).

Anal. calc'd for $C_{24}H_{17}FN_4O_2 \cdot 0.1C_4H_{10}O$:
C, 69.80; H, 4.32; N, 13.34;
Found: C, 69.50; H, 4.43; N, 13.44.

EXAMPLE 163

1,3-Dihydro-5-phenyl-3(RS)-(4-n-propylbenzoylamino)-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(RS)-amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (39.2 mg, 0.156 mmole) in place of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-

benzodiazepin-2-one and 4-n-propylbenzoyl chloride (28.5 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The product was chromatographed on silica gel (15% (v/v) Et_2O in CH_2Cl_2 elution). The combined product fractions were evaporated to dryness in vacuo and crystallized from Et_2O to give the title compound which was dried in vacuo at 82°C: (m.p.. 158-162°C).

TLC: Single spot, R_f=0.24, silica gel plate, 15% (v/v) Et_2O in CH_2Cl_2.

NMR: Consistent with structure.

HPLC: Greater than 99% pure.

MS: Molecular ion at m/e=397.

Anal. calc'd for $C_{25}H_{23}N_3O_2$:

C, 75.54; H, 5.83; N, 10.57;

Found: C, 75.16; H, 5.98; N, 10.74.

EXAMPLE 164

1,3-Dihydro-5-phenyl-3(RS)-(4-phenylbenzoylamino)-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(RS)-amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (39.2 mg, 0.156 mmole) in place of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one and 4-phenylbenzoyl chloride (33.8 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The product was chromatographed on silica gel (15% (v/v) Et_2O in CH_2Cl_2 elution). The combined product fractions were evaporated to dryness in vacuo and crystallized from Et_2O to give the title compound which was dried in vacuo at 82°C: (m.p. 274-276°C).

TLC: Single spot, R_f=0.24, silica gel plate, 15% (v/v) Et_2O in CH_2Cl_2.
NMR: Consistent with structure.
HPLC: Greater than 98% pure.
MS: Molecular ion at m/e=431.
Anal. calc'd for $C_{28}H_{21}N_3O_2$:
C, 77.94; H, 4.91; N, 9.74;
Found: C, 77.69; H, 5.17; N, 9.84.

EXAMPLE 165

1,3-Dihydro-3(RS)-(4-n-pentylbenzoylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(RS)-amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (39.2 mg, 0.156 mmole) in place of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one and 4-n-pentylbenzoyl chloride (32.9 mg, 0.156 mmole) in place of p-trifluorobenzoyl chloride. The product was chromatographed on silica gel (15%, (v/v) Et_2O in CH_2Cl_2 elution). The combined product fractions were evaporated to dryness in vacuo and crystallized from Et_2O to give the title compound which was dried in vacuo at 82°C: (m.p. 203-205°C).
TLC: Single spot, R_f=0.28, silica gel plate, 15% (v/v) Et_2O in CH_2Cl_2.
NMR: Consistent with structure.
HPLC: Greater than 99% pure.
MS: Molecular ion at m/e=425.
Anal. calc'd for $C_{27}H_{27}N_3O_2$:
C, 76.21; H, 6.40; N, 9.88;
Found: C, 76.07; H, 6.53; N, 10.00.

EXAMPLE 166

1,3-Dihydro-3(RS)-(1-naphthoylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(RS)-amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (39.2 mg, 0.156 mmole) in place of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one and 1-naphthoyl chloride (29.7 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The product was chromatographed on silica gel (15% (v/v) Et_2O in CH_2Cl_2 elution). The combined product fractions were evaporated to dryness *in vacuo* and crystallized from Et_2O to give the title compound which was dried *in vacuo* at 65°C: (m.p. 162-167°C).

TLC: Single spot, R_f=0.22, silica gel plate, 15% (v/v) Et_2O in CH_2Cl_2.

NMR: Consistent with structure.

HPLC: Greater than 96% pure.

MS: Molecular ion at m/e=405.

Anal. calc'd for $C_{26}H_{19}N_3O_2$:

C, 77.02; H, 4.72; N, 10.37;

Found: C, 77.20; H, 4.91; N, 10.25.

EXAMPLE 167

3(S)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(3-iodobenzoylamino)-1-methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(S)-(-)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one (44.2 mg, 0.156 mmole) in place of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one and 3-iodobenzoyl chloride (41.6 mg, 0.156 mmole) in

place of p-trifluoromethylbenzoyl chloride. The product was chromatographed on silica gel (5% (v/v) Et_2O in CH_2Cl_2 elution). The combined product fractions were evaporated to dryness in vacuo to give the title compound which was dried in vacuo at 65°C: (m.p. 105-120°C).

TLC: Single spot, R_f=0.34, silica gel plate, 5% (v/v) Et_2O in CH_2Cl_2.

NMR: Consistent with structure.

HPLC: Greater than 96% pure.

MS: Molecular ion at m/e=513.

$[\alpha]_D^{25}$ = +13.0° (0.0024 g/ml, CH_2Cl_2).

Anal. calc'd for $C_{23}H_{17}FIN_3O_2$:

C, 53.82; H, 3.34; N, 8.19;

Found: C, 54.10; H, 3.46; N, 8.18.

EXAMPLE 168

3(R)-(-)-1,3-Dihydro-5-(2-fluorophenyl)-3-(3-iodobenzoylamino)-1-methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(R)-(+)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one (44.2 mg, 0.156 mmole) in place of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one and 3-iodobenzoyl chloride (41.6 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The product was chromatographed on silica gel (5% (v/v) Et_2O in CH_2Cl_2 elution). The combined product fractions were evaporated to dryness in vacuo to give the title compound which was dried in vacuo at 65°C: (m.p. 169-172°C).

TLC: Single spot, R_f=0.38, silica gel plate, 5% (v/v) Et_2O in CH_2Cl_2.

NMR: Consistent with structure.
HPLC: Greater than 97% pure.
MS: Molecular ion at m/e=513.
$[\alpha]_D^{25}$ = -10.2° (0.0026 g/ml, CH_2Cl_2).
Anal. calc'd for $C_{23}H_{17}FIN_3O_2$:
C, 53.82; H, 3.34; N, 8.19;
Found: C, 54.07; H, 3.42; N, 8.50.

EXAMPLE 169

3(R)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(2-iodobenzoylamino)-1-methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(R)-(+)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one (44.2 mg, 0.156 mmole) in place of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one, and 2-iodobenzoyl chloride (41.6 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The product was chromatographed on silica gel (5% (v/v) Et_2O in CH_2Cl_2 elution). The combined product fractions were evaporated to dryness in vacuo and crystallized from ether to give the title compound which was dried in vacuo at 65°C: (m.p. 231-235°C).
TLC: Single spot, R_f=0.24, silica gel plate, 5% (v/v) Et_2O in CH_2Cl_2.
NMR: Consistent with structure.
HPLC: Greater than 99% pure.
MS: Molecular ion at m/e=513.
$[\alpha]_D^{25}$ = +26.1° (0.0028 g/ml, CH_2Cl_2).
Anal. calc'd for $C_{23}H_{17}FIN_3O_2$:
C, 53.82; H, 3.34; N, 8.19;
Found: C, 53.71; H, 3.38; N, 8.14.

EXAMPLE 170

3(S)-(-)-1,3-Dihydro-5-(2-fluorophenyl)-3-(2-iodobenzoylamino)-1-methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(S)-(-)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one (44.2 mg, 0.156 mmole) in place of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one and 2-iodobenzoyl chloride (41.6 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The product was chromatographed on silica gel (5% (v/v) Et_2O in CH_2Cl_2 elution). The combined product fractions were evaporated to dryness in vacuo and crystallized from Et_2O to give the title compound which was dried in vacuo at 65°C: (m.p. 230-232°C).
TLC: Single spot, R_f=0.24, silica gel plate, 5% (v/v) Et_2O in CH_2Cl_2.
NMR: Consistent with structure.
HPLC: Greater than 98% pure.
MS: Molecular ion at m/e=513.
$[\alpha]_D^{25}$ = -25.6° (0.0029 g/ml, CH_2Cl_2).
Anal. calc'd for $C_{23}H_{17}FIN_3O_2$:
C, 53.82; H, 3.34; N, 8.19;
Found: C, 53,62; H, 3.25; N, 8.30.

EXAMPLE 171

3(R)-(+)-3-(2-Bromobenzoylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(R)-(+)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one (44.2 mg, 0.156 mmole) in place of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one and

2-bromobenzoyl chloride (34.2 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The product was chromatographed on silica gel (5% (v/v) Et_2O in CH_2Cl_2 elution). The combined product fractions were evaporated to dryness in vacuo and crystallized from Et_2O to give the title compound which was dried in vacuo at 65°C: (m.p. 155-160°C). TLC: Single spot, R_f=0.28, silica gel plate, 5% (v/v) Et_2O in CH_2Cl_2. NMR: Consistent with structure. HPLC: Greater than 99% pure. MS: Molecular ion at m/e=465. $[\alpha]_D^{25}$ = +26.3° (0.0034 g/ml, CH_2Cl_2). Anal. calc'd for $C_{23}H_{17}BrFN_3O_2$:

C, 59,24; H, 3.67; N, 9.01;

Found: C, 59.15; H, 3.70; N, 9.12.

EXAMPLE 172

3(R)-(+)-3-(2-Chlorobenzoylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 3(R)-(+)-3-amino-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one (44.2 mg, 0.156 mmole) in place of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one and 2-chlorobenzoyl chloride (27.3 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The product was chromatographed on silica gel (5% (v/v) Et_2O in CH_2Cl_2 elution). The combined product fractions were evaporated to dryness in vacuo and crystallized from CH_2Cl_2 to give the title compound which was dried in vacuo at 65°C: (m.p. 157-165°C).

TLC: Single spot, R_f=0.25, silica gel plate, 5% (v/v) Et_2O in CH_2Cl_2.
NMR: Consistent with structure.
HPLC: Greater than 99% pure.
MS: Molecular ion at m/e=421.
$[\alpha]_D^{25}$ = +16.7° (0.0032 g/ml, CH_2Cl_2).
Anal. calc'd for $C_{23}H_{17}ClFN_3O_2$:
C, 65.48; H, 4.06; N, 9.96;
Found: C, 65.63; H, 4.10; N, 10.03.

EXAMPLE 173

1,3-Dihydro-5-(2-fluorophenyl)-3(RS)-phenylcarbonylamino-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using benzoyl chloride (21.9 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The title compound was crystallized from ethyl acetate and dried in vacuo at 75°C: (m.p. 243-244°C).
TLC: Single spot, R_f=0.18, silica gel plate, (chloroform-methanol, 1:1 v/v).
NMR: The spectrum was consistent with the title structure.
HPLC: Greater than 98% pure.
MS: Molecular ion at m/e=373.
Anal. calc'd for
C, 70.76; H, 4.32; N, 11.25;
Found: C, 70.63; H, 4.35; N, 11.07.

EXAMPLE 174

1,3-Dihydro-5-(2-fluorophenyl)-3(RS)-(2-chlorophenyl)-carbonylamino-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using 2-chlorobenzoyl chloride (27.3 mg, 0.156 mmole)

in place of p-trifluoromethylbenzoyl chloride. The title compound was crystallized from ethyl acetate and dried in vacuo at 75°C: (m.p. 224-224.5°C).
TLC: Single spot, R_f=0.27, silica gel plate, (chloroform-methanol, 97:3 v/v).
NMR: The spectrum was consistent with the title structure.
HPLC: Greater than 98% pure.
MS: Molecular ion at m/e=407.
Anal. calc'd for $C_{22}H_{15}ClFN_3O_2 \cdot 0.1C_4H_8O_2$:
C, 64.57; H, 3.82; N, 10.08;
Found: C, 64.30; H, 3.76; N, 9.99.

EXAMPLE 175

1,3-Dihydro-5-(2-fluorophenyl)-3(RS)-benzyloxycarbonylamino-2H-1,4-benzodiazepin-2-one

The procedure of Example 134 was carried out using benzyl chloroformate (26.6 mg, 0.156 mmole) in place of p-trifluoromethylbenzoyl chloride. The title compound was crystallized from ethyl acetate and dried in vacuo at 75°C: (m.p. 208°C).
TLC: Single spot, R_f=0.37, silica gel plate, (hexane-ethyl acetate, 1:1 v/v).
NMR: The spectrum was consistent with the title structure.
HPLC: Greater than 98% pure.
MS: Molecular ion at m/e=403.
Anal. calc'd for $C_{23}H_{18}FN_3O_3$:
C, 68.48; H, 4.50; N, 10.42;
Found: C, 68.84; H, 4.62; N, 10.49.

EXAMPLE 176

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-benzyloxycarbonylamino-2H-1,4-benzodiazepin-2-thione

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-benzyloxycarbonylamino-2H-1,4-benzodiazepin-2-one (6.5 g, 16.1 mmole) and 2,4-bis-(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiaphosphetane (4.9 g, 12.1 mmole) were combined in 500 ml of toluene and heated at reflux for 1.5 hours. The reaction mixture was cooled, diluted to 700 ml with ethyl acetate and washed with 10% sodium hydroxide solution (4 x 50 ml) and brine. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to yield 12 g of crude product. Trituration with ethyl acetate gave 4.0 g of the analytical product as a yellow powder. Chromatography of the mother liquors on silica gel (hexane-ethyl acetate elution, 1:1 v/v) afforded an additional 2.2 g of pure product: m.p. 190-191°C.

NMR ($CDCl_3$): Confirmed structure of the title compound.

MS (14 ev): 419 (M^+), 311, 284, 256, 243, 224.

Anal. calc'd for $C_{23}H_{18}FN_3O_2S$:

N, 10.02; C, 65.86; H, 4.33;

Found: N, 9 79; C, 65.59; H, 4.44.

EXAMPLE 177

1-(4-Chlorophenyl)carbonyl-1,3-dihydro-5-(2-fluorophenyl)-3(RS)-(4-chlorophenyl)carbonylamino-2H-1,4-benzodiazepin-2-one

To a solution of 1,3-dihydro-5-(2-fluorophenyl)-3-amino-2H-1,4-benzodiazepin-2-one (400 mg, 1.49 mmole) in 25 ml of methylene chloride was added

p-chlorobenzoyl chloride (380 µl, 3.0 mmole). Triethylamine was added to bring the pH of the reaction mixture to approximately 6 (moist pH paper) followed by 4-dimethylamino pyridine (183 mg, 1.5 mmole). After stirring at room temperature overnight the reaction mixture was diluted with methylene chloride to 200 ml and washed in succession with 10% citric acid solution (3 x 50 ml), saturated sodium bicarbonate solution, and brine. The organic extracts were dried ($MgSO_4$) and concentrated to give 890 mg of crude product. Silica gel chromatography (hexane-ethyl acetate, 1:1 v/v) afforded the analytical product: m.p. 190-191°C.

TLC: Single spot, R_f=0.70, silica gel (hexane-ethyl acetate, 1:1 v/v).

NMR: The spectrum is consistent with the title structure.

HPLC: Greater than 97% pure.

MS: Molecular ion m/e=546.

Anal. calc'd for $C_{29}H_{18}Cl_2FN_3O_3$:
N, 7.69; C, 63.74; H, 3.32;
Found: N, 7.58; C, 63.88; H, 3.46.

EXAMPLE 178

1-(4-Chlorophenyl)carbonyl-1,3-dihydro-5-(2-fluorophenyl)-3(RS)-(4-chlorophenyl)carbonyloxy-2H-1,4-benzodiazepin-2-one

A suspension of 1,3-dihydro-5-(2-fluorophenyl)-3-hydroxy-2H-1,4-benzodiazepin-2-one (610 mg, 2.25 mmole) in 25 ml of methylene chloride was treated with 4-chlorobenzoyl chloride (0.314 ml, 2.48 mmole) at room temperature. 4-Dimethylaminopyridine (303 mg, 2.48 mmole) was added and within minutes the

reaction mixture became homogeneous. The reaction mixture was protected from moisture and stirred at room temperature overnight. An additional equivalent each of 4-chlorobenzoyl chloride and 4-dimethylaminopyridine were added and stirring was continued for 8 hours at 40-45°C. The reaction mixture was diluted to 150 ml with methylene chloride and washed in succession with 10% citric acid solution (3 x 50 ml), saturated sodium bicarbonate solution (3 x 50 ml) and brine (50 ml). Rotoevaporation of the dried ($MgSO_4$) organic phase gave a foam which on trituration with ether afforded a beige solid. Recrystallization from ethyl acetate afforded 612 mg of the title compound as a white powder in analytical purity: m.p. 198-199°C.

NMR (DMSO-d_6): The spectrum is consistent with the title structure.

MS (14 ev): 547 (M^+), 407, 379, 374, 363, 224, 156.

Anal. calc'd for $C_{29}H_{17}Cl_2FN_2O_4$:

N, 5.11; C, 63.63; H, 3.13;

Found: N, 5.03; C, 63.68; H, 3.08.

EXAMPLE 179

1,3-Dihydro-5-(2-fluorophenyl)-3(RS)-(4-chlorophenyl)-oxy-2H-1,4-benzodiazepin-2-one

A suspension of 1,3-dihydro-5-(2-fluorophenyl)-3-hydroxy-2H-1,4-benzodiazepin-2-one (610 mg, 2.25 mmole) in 25 ml of methylene chloride was treated with 4-chlorobenzoyl chloride (0.314 ml, 2.48 mmole) at room temperature. 4-Dimethylaminopyridine (303 mg, 2.48 mmole) was added and within minutes the reaction mixture became homogeneous. The reaction mixture was protected from moisture and stirred at

room temperature overnight. An additional equivalent each of 4-chlorobenzoyl chloride and 4-dimethylaminopyridine were added and stirring was continued for 8 hours at 40-45°C. The reaction mixture was diluted to 150 ml with methylene chloride and washed in succession with 10% citric acid solution (3 x 50 ml), saturated sodium bicarbonate solution (3 x 50 ml) and brine (50 ml). Rotoevaporation of the dried ($MgSO_4$) organic phase gave a foam which on trituration with ether afforded a beige solid. The mother liquors were concentrated and the residue chromatographed on silica gel (hexane-ethyl acetate, 1:1 v/v) to give the title compound.

NMR ($CDCl_3$): The spectrum is consistent with the title structure.

Anal. calc'd for $C_{22}H_{14}ClFN_2O_3$:
N, 6.85; C, 64.63; H, 3.45;
Found: N, 6.68; C, 64.64; H, 3.60.

EXAMPLE 180

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-(4-chlorophenyl)carbonylamino-2H-1,4-benzodiazepin-2-thione

A mixture of 1,3-dihydro-5-(2-fluorophenyl)-3-(RS)-amino-2H-1,4-benzodiazepin-2-thione (200 mg, 0.70 mmole), 4-chlorobenzoic acid (120 mg, 0.77 mmole) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (150 mg, 0.77 mmole) were combined in 2 ml of dry N,N-dimethylformamide at room temperature. The pH of the homogeneous reaction mixture was then adjusted to 8 with triethylamine. The reaction mixture was protected from moisture and stirred at room temperature overnight (about 90% complete after 1 hour). The solvent was removed

under reduced pressure and the residue dissolved in 100 ml of ethyl acetate. The organic phase was then washed in succession with 10% citric acid solution (2 x 20 ml), saturated sodium bicarbonate solution (20 ml), and brine. The dried ($MgSO_4$) organic phase was rotoevaporated to dryness to yield 300 mg of crude product. Preparative thick layer chromatography on SiO_2 (hexane-ethyl acetate, 2:1) gave the analytical sample as a solvate: m.p. 156-158°C.

NMR (DMSO-d_6): Confirmed structure of the title compound.

MS (14 ev): 423 (M^+), 391, 284, 268, 236, 139.

Anal. calc'd for $C_{22}H_{15}ClFN_3OS$. $0.10C_4H_8O_2$:

N, 9.71; C, 62.17; H, 3.68;

Found: N, 9.39; C, 62.45; H, 4.01.

EXAMPLE 181

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-(2-indole) carbonylamino-2H-1,4-benzodiazepin-2-thione

A mixture of 1,3-dihydro-5-(2-fluorophenyl)-3-(RS)-amino-2H-1,4-benzodiazepin-2-thione (400 mg, 1.40 mmole), indole-2-carboxylic acid (248 mg, 1.54 mmole) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (295 mg, 1.54 mmole) were combined in 10 ml of dry N,N-dimethylformamide at room temperature. The pH of the homogeneous reaction mixture was then adjusted to 8 with triethylamine. The reaction mixture was protected from moisture and stirred at room temperature overnight (about 50% complete after 1 hour). The solvent was removed under reduced pressure and the residue dissolved in 200 ml of ethyl acetate. The organic phase was then

washed in succession with 10% citric acid solution (2 x 25 ml), saturated sodium bicarbonate solution (25 ml), and brine. The dried ($MgSO_4$) organic phase was rotoevaporated to dryness to yield 1.4 g of crude product. Preparative thick layer chromatography on SiO_2 (hexane-ethyl acetate, 1:1) gave the analytical sample as a beige powder: m.p. 209-211°C. NMR ($CDCl_3$): Confirmed structure of the title compound.

MS (14 ev): 428 (M^+), 396, 394, 296, 293, 252, 249.

Anal. calc'd for $C_{24}H_{17}FN_4OS.\ 0.15C_4H_8O_2$:
N, 12.69; C, 66.89; H, 4.15;
Found: N, 12.92; C, 66.69; H, 3.90.

EXAMPLE 182

1,3-Dihydro-3(RS)-(4-chlorophenyl)aminocarbonylamino-2H-1,4-benzodiazepin-2-one

To a solution of 85 mg (0.315 mmole) of 1,3-dihydro-3(RS)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one in 8 ml of dry tetrahydrofuran was added 4-chlorophenylisocyanate (40 µl, 0.315 mmole) at room temperature. Within 15 minutes a flocculant, white precipitate formed. Stirring was continued for 8 hours more and the reaction mixture was filtered. The collected solids were washed with hot methanol and dried in vacuo to give the analytical product: m.p. 278°C.
NMR (DMSO-d_6): Confirms structure assignment of product.

Anal. calc'd for $C_{22}H_{16}ClFN_4O_2$:
N, 13.25; C, 62.48; H, 3.81;
Found: N, 13.09; C, 62.33; H, 3.86.

EXAMPLE 183

1-3-Dihydro-1-methyl-3-oximino-5-phenyl -2H-1,4-benzodiazepin-2-one

To a suspension of potassium tert-butoxide (24.9 g, 222 mmole) in 600 ml of dry tetrahydrofuran was added 200 ml of dry tert-butylalcohol at -20°C under nitrogen. To this solution was then added via addition funnel 1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (25 g, 99.9 mmole) in 260 ml of tetrahydrofuran. The resulting wine colored solution was stirred for 2 hours at -20°C and treated with 17.4 ml (130 mmole) of isoamyl nitrite. The reaction mixture was warmed to 0°C over 15 minutes and quenched with the addition of 60 ml of cold water and 20 ml of glacial acetic acid. All solvents were removed under reduced pressure and the residue was partitioned between ethyl acetate (600 ml) and brine (100 ml). The phases were separated and the organic extracts were dried (Na_2SO_4) and concentrated. The resulting semi-solid was triturated with ether to give 21 g of off-white solid. m.p. 234-235°C; R_f=0.15 (ethylacetate-hexane, 1:1); R_f=0.28 chloroform-ethanol, 95:5);

ir(KBr, partial): 3300, 1650, 1595, 1320, 1205, 1030, 975 cm^{-1}.

MS (14 ev.): 279 (M^+), 262, 249, 236, 222.

NMR ($CDCl_3$): 3.5 (3H, CH_3-N), confirms structure assignment.

Elemental Analysis: $C_{16}H_{13}N_3O_2$.

Calcd: C, 4.69; H, 68.81; N, 15.04.

Found: C, 4.62; H, 68.67; N, 15.08.

EXAMPLE 184

3(R S)-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

A solution of 150 ml of methanol containing 5 g (17.9 mmole) of 1,3-dihydro-1-methyl-3-oximino-5-phenyl-1,4-benzodiazepin-2-one was treated with a slurry of active Raney-nickel catalyst[1] in ethanol (10 g). The resulting suspension was hydrogenated on a Parr apparatus at 60 psi and 23°C for 30 hours. The catalyst was removed by filtration and the filtrate was concentrated to afford the title compound in 95% yield.

R_f=0.23 (chloroform-ethanol, 95:5), R_f=0.23 (chloroform-methanol-acetic acid-water, 90:10:1:1)

NMR ($CDCl_3$): spectrum confirms structure assignment.

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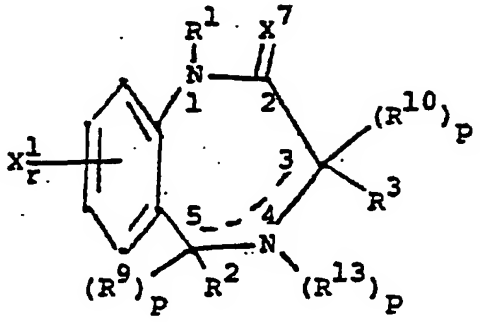
[1] Raney-Nickel catalyst was prepared according to Fieser & Fieser, Reagents for Organic Synthesis, Vol. I, John Wiley & Sons, Inc., New York 1967, p. 729.

Claims to the invention follow.

WHAT IS CLAIMED IS:

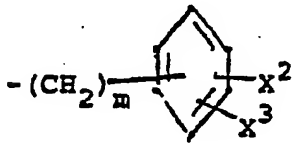
1. A compound of Formula I:



I

wherein
R^1 is H, C_1-C_5 linear or branched alkyl, /loweralkenyl, loweralkynyl, $-(CH_2)_mCOOR^6$, $-(CH_2)_n$-cycloloweralkyl, $-(CH_2)_mNR^4R^5$, $-(CH_2)_mCONR^4R^5$, $-(CH_2)_mCN$, or $-(CH_2)_nCX_3^{10}$;

R^2 is H, loweralkyl, substituted or unsubstituted phenyl (wherein the substitutents may be 1 or 2 of halo, loweralkyl, loweralkoxy, loweralkylthio, carboxyl, carboxyloweralkyl, nitro, $-CF_3$, or hydroxy),



$-(CH_2)_mSCH_3$, $-(CH_2)_mSOCH_3$, $-(CH_2)_mSO_2CH_3$, or $-(CH_2)_mCOOR^6$;

R^3 is $-(CH_2)_nR^7$, $-(CH_2)_nCHR^7$, $-(CH_2)_n-C(OH)-R^7$ (R_a^7)

Dr.IM.-vd
19.6.1985

$-(CH_2)_n\overset{O}{\overset{\|}{C}}R^7$, $-(CH_2)_nNR^{18}(CH_2)_qR^7$,

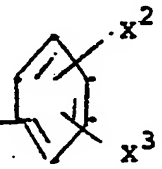
$-(CH_2)_nNR^{18}\underset{(CH_2)_q}{\overset{R^7}{|}}CHCOOR^6$,

$-(CH_2)_nX^9\overset{O}{\overset{\|}{C}}(CH_2)_qR^7$,

$-NH(CH_2)_{2-3}NHR^7$, $-NH(CH_2)_{2-3}NHCOR^7$,

$-(CH_2)_nX^9\overset{O}{\overset{\|}{C}}CH\underset{NHCOOR^{14}}{\overset{CH_2R^7}{|}}$,

$-(CH_2)_nX^9\overset{O}{\overset{\|}{C}}X_a^9(CH_2)_nR^7$, $-(CH_2)_nX^9\overset{O}{\overset{\|}{C}}-\underset{}{\overset{NH_2}{CH}}-CH_2R^7$,

$-(CH_2)_nX^9\overset{O}{\overset{\|}{C}}(CH_2)_qX_a^9$ 

$-(CH)_2)_nNR^{18}SO_2(CH_2)_qR^7$ or

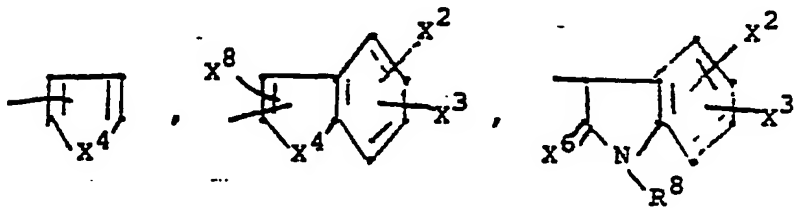
$-CHR^7$

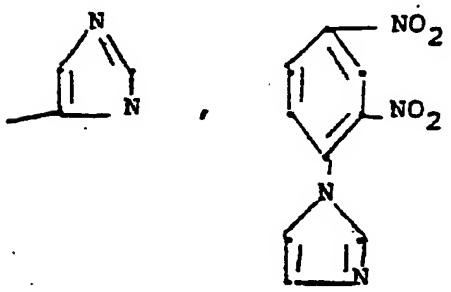
R^4 and R^5 are independently H, loweralkyl, or cycloloweralkyl;

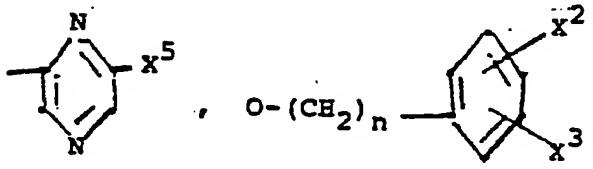
R^6 is H, loweralkyl, cycloloweralkyl, substituted or unsubstituted phenyl, or substituted or

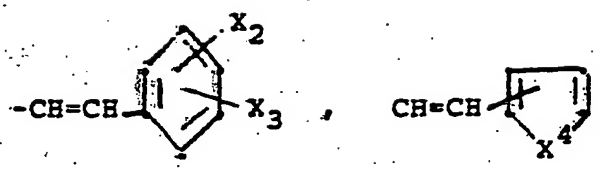
unsubstituted phenylloweralkyl wherein the phenyl or phenylloweralkyl substituents may be 1 or 2 of halo, loweralkyl, loweralkoxy, nitro, or CF_3;

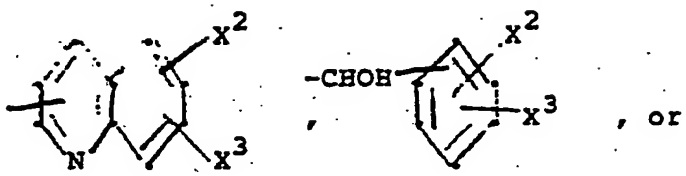
R^7 and R_a^7 are independently α- or β-naphthyl, substituted or unsubstituted phenyl wherein the substituents may be 1 to 2 of halo, $-NO_2$, -OH, $-NR^4R^5$, loweralkyl, CF_3, CN, SCF_3, C≡CH, CH_2SCF_3, $OCCH_3$ (O), $OCHF_2$, SH, SPh, PO_3H, loweralkoxy, or loweralkylthio,

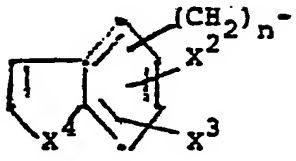






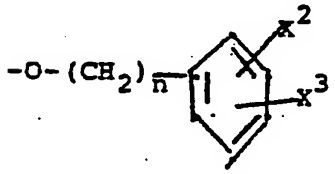






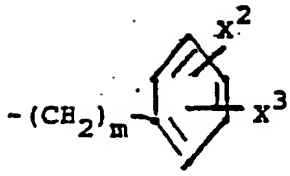
with the provisos that q is not 0 or 1 in $-(CH_2)_nNH(CH_2)_qR^7$ and that q is not 0 in

when R^7 or R_a^7 is



;

R^8 is H, loweralkyl, cycloloweralkyl, $-(CH_2)_mCONH_2$, $-(CH_2)_mCOOR^6$, $-(CH_2)_m$-cycloloweralkyl, $-(CH_2)_mNR^4R^5$,



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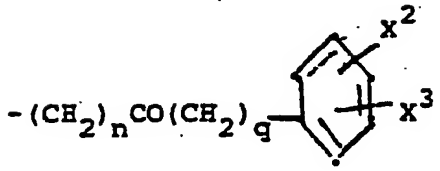
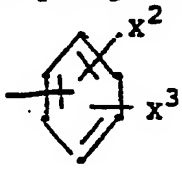
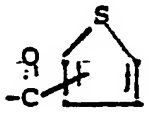


, or

$-COCHNHCOOR^{11}$;
CH_2R^{12}

R^9 and R^{10} are independently H, -OH, or $-CH_3$;
R^{11} and R^{12} are independently loweralkyl or cycloloweralkyl;
R^{13} is H, loweralkyl, acyl, O, or cycloloweralkyl;
R^{14} is loweralkyl or phenylloweralkyl;

R^{15} is H, loweralkyl,  , or $-NR^{16}R^{17}$;

R^{16} and R^{17} are independently H, or  ;

R^{18} is H, loweralkyl, or acyl;
m is 1-4;
n is 0-4;

p is 0 when its adjacent --- is unsaturated and
1 when its adjacent --- is saturated except
that when R^{13} is O, p = 1 and --- is unsaturated;

q is 0-4;

r is 1 or 2;

X^1 is H, $-NO_2$, CF_3 CN, OH, loweralkyl, halo, loweralkylthio, loweralkoxy, $-(CH_2)_nCOOR^6$, or $-NR^4R^5$;

X^2 and X^3 are independently H, $-OH$, $-NO_2$, halo, loweralkylthio, loweralkyl, or loweralkoxy;

X^4 is S, O, CH_2, or NR^8;

X^5 is H, CF_3, CN, $-COOR^6$, NO_2, or halo;

X^6 is O or HH;

X^7 is O, S, HH, or NR^{15} with the proviso that X^7 can be NR^{15} only when R^1 is not H;

X^8 is H, loweralkyl;

X^9 and X_a^9 are independently NR^{18}, O;

X^{10} is F, Cl, or Br.

--- is a saturated or unsaturated bond

and salts and quaternary ammonium salts of the compounds of formula I.

2. A compound of Claim 1 wherein:

R^1 is H, loweralkyl, or $-(CH_2)_mCOOR^6$;

R^2 is substituted or unsubstituted phenyl (wherein the substituents may be 1 or 2 of halo, loweralkyl, loweralkoxy, carboxyl, carboxyloweralkyl, nitro, $-CF_3$, or hydroxy), or $-(CH_2)_mCOOR^6$;

R^3 is $-(CH_2)_nR^7$, $-(CH_2)_n\overset{OH}{\overset{|}{C}}HR^7$, $-(CH_2)_n\overset{O}{\overset{\|}{C}}R^7$, $-(CH_2)_nNH(CH_2)_qR^7$,

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$-(CH_2)_nNHCHCOOR^6$ (with R^7 and $(CH_2)_q$), $-(CH_2)_nNHC(CH_2)_qR^7$,

$-NH(CH_2)_{2-3}NHR^7$, $-(CH_2)_nNHCCHCH_2R^7$ (with $NHCOOR^{14}$),

$-NH(CH_2)_{2-3}NHCOR^7$, or $-(CH_2)_nNHCNH(CH_2)_nR^7$;

R^4 and R^5 are independently H or loweralkyl;

R^6 is H or loweralkyl;

R^7 is α- or β-naphthyl,

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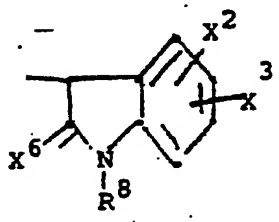

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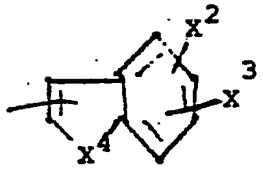
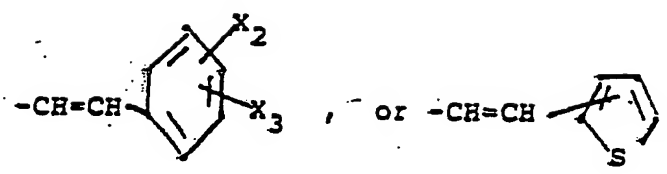


,

substituted or unsubstituted phenyl (wherein the substituents may be 1 to 2 of halo, $-NO_2$, $-OH$, $-NR^4R^5$, loweralkyl, CF_3, loweralkoxy, lower alkylthio, CN, $-C{\equiv}CH$, SCF_3, $OCCH_3$, $OCHF_2$, or SPh,



R^8 is H, loweralkyl, or $-COCHNHCOOR^{11}$ (CH_2R^{12});

R^9 and R^{10} are independently H, -OH, or $-CH_3$;
R^{11} and R^{12} are independently loweralkyl;
R^{13} is H, O, loweralkyl or acyl;
R^{14} is loweralkyl;
R^{15} is H or lower alkyl;

m is 1-4;
n is 0-4;
p is 0 when its adjacent --- is unsaturated and 1 when its adjacent --- is saturated except that when R^{13} is O, p=1 and --- is unsaturated;
q is 0-4;
r is 1 or 2;
X^1 is H, $-NO_2$, CF_3, CN, OH, loweralkyl, halo, loweralkylthio, loweralkoxy, $-(CH_2)_nCOOR^6$, or $-NR^4R^5$;
X^2 and X^3 are independently H, -OH, $-NO_2$, halo, loweralkylthio, loweralkyl, or loweralkoxy;
X^4 is S, O, or NR^8;
X^6 is O or HH;
X^7 is O;
--- is a saturated or unsaturated bond

and salts and quaternary ammonium salts of said compounds.

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3. A compound of Claim 2 wherein:

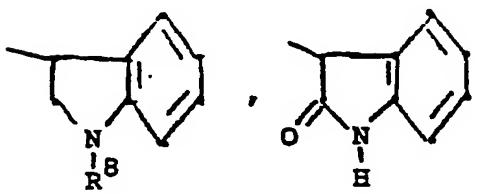
R^1 is H, methyl, ethyl, carboxymethyl, or ethylcarboxymethyl;

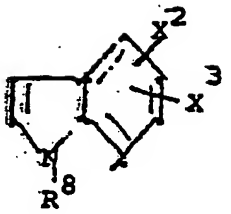
R^2 is substituted or unsubstituted phenyl wherein the substitutents may be 1 or 2 of halo or carboxyl, or $-(CH_2)_{1-2}COOR^6$;

R^3 is $-(CH_2)_nR^7$, $-(CH_2)_nCHR^7$ (OH), $-(CH_2)_nCR^7$ (O), $-(CH_2)_nNH(CH_2)_qR^7$, $-(CH_2)_nNHCHCOOR^6$ ($CH_2)_q$ R^7, $-(CH_2)_nNHCCHCH_2R^7$ (O; $NHCOOR^{14}$), or $-(CH_2)_nNHC(CH_2)_qR^7$ (O);

R^6 is H or loweralkyl;

R^7 is α- or β-naphthyl,





substituted phenyl (wherein the substituents may be 1 or 2 of halo, loweralkyl, or CF_3)

or -CH=CH- 

R^8 is H, methyl, or ethyl;

R^9 and R^{10} are independently H, -OH, or $-CH_3$;
R^{13} is H, methyl or formyl;
R^{14} is t-butyl;
n is 0-4;
p is 0 when its adjacent --- is unsaturated and 1 when its adjacent --- is saturated;
q is 0-4;
r is 1 or 2;
X^1 is H, $-NO_2$, CF_3, CN, OH, or halo;
X^2 and X^3 are independently H, -OH, $-NO_2$, or halo;
X^7 is O;
--- is a saturated or unsaturated bond

and salts and quaternary ammonium salts of said compounds.

4. A compound of Claim 2 wherein:
R^1 is H, methyl, or carboxymethyl;

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R^2 is phenyl, o-fluorophenyl, p-fluorophenyl, o-chlorophenyl, p-chlorophenyl, o-carboxyphenyl, 2,4-dichlorophenyl, 2,6-difluorophenyl, $-CH_2COOEt$, $-CH_2COO\text{-}t\text{-}Bu$, $-CH_2CH_2COOEt$, or $-CH_2CH_2COO\text{-}t\text{-}Bu$;

R^3 is $-(CH_2)_{1-2}R^7$, $-\overset{OH}{\underset{|}{C}}HR^7$,

$-\overset{O}{\overset{\|}{C}}R^7$, $-(CH_2)_{0-1}NH(CH_2)_{1-2}R^7$,

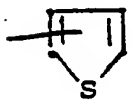
$-(CH_2)_{0-1}\overset{R^7}{\underset{|}{N}}HCHCOOR^6$, $-(CH_2)_{0-1}NH\overset{O}{\overset{\|}{C}}(CH_2)_{0-2}R^7$, or

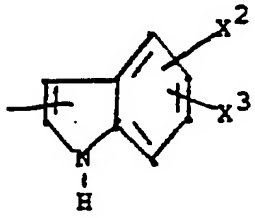
$-(CH_2)_{0-1}NHCOCHCH_2R^7$ (NHCOOR^{14}),

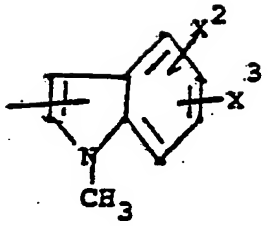
and the stereochemistry relates to D-tryptophan;

R^6 is H, methyl, or ethyl;

R^7 is α- or ß-naphthyl,







mono or dihalo phenyl,

R^9 and R^{10} are independently H or -OH,
R^{13} is H;
R^{14} is t-butyl;
p is 0 when its adjacent --- is unsaturated and 1 when its adjacent --- is saturated;
r is 1;
X^1 is H, 7-chloro, 7-fluoro, or 7-nitro;
X^2 and X^3 are independently H, -OH, fluoro, or chloro;
X^7 is O;
--- is a saturated or unsaturated bond
and salts and quaternary ammonium salts of said compoundd.

5. A compound of Claim 1 which is:

1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3(R)-[3'-(1'-methyl-indolyl)-methyl]-1-methyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)-methyl-1-methyl-2H-1,4-benzodiazepin-2-one

7-chloro-1,3-dihydro-3(R)-(3'-indolyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(R)-(3'-indolyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

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1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-α-indolenyl) methyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-β-indolenyl) methyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-thione;

1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepine;

7-chloro-1,3-dihydro-3(R)-benzyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

3(R)-benzyloxymethyl-7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one;

7-chloro-1,3-dihydro-3(RS)-(1-naphthyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

7-chloro-1,3-dihydro-3(RS)-(2-naphthyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3(RS)-(2-thienyl)methyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3(RS)-(3-thienyl)-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3(R)-[3'-β-(1'-t-Boc-L-leucyl)-indolenyl]methyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3(R)-[3'-β-(1'-t-Boc-D-leucyl)-indolenyl]methyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3(R)-[3'-α-(1'-t-Boc-L-leucyl)-indolenyl]methyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3(R)-[3'-α-(1'-t-Boc-D-leucyl)-indolenyl]methyl-2H-1,4-benzodiazepin-2-one;

7-chloro-1,3,4,5-tetrahydro-3(R)-(3'-indolyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

7-chloro-1,3,4,5-tetrahydro-3(S)-(3'-indolyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

4-(p-chlorobenzoyl)-5-(2-fluorophenyl)-3(R)-[3'-(1'-methylindolyl)-methyl]-1-methyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one;

4-acetyl-5-(2-fluorophenyl)-3(R)-[3'-(1'-methylindolyl)-methyl]-1-methyl-1,3,4,5-tetrahydro-2H-1,4-benzodiazepin-2-one;

7-chloro-5-(2-chlorophenyl)-1,3-dihydro-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(R)-(3'-indolyl)methyl-5-methyl-2H-1,4-benzodiazepin-2-one;

1-benzyl-7-chloro-1,3-dihydro-3(R)-(3'-indolyl)-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

7-chloro-1,3-Dihydro-3(R)-(3'-indolyl)methyl-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3(S)-(3'-indolyl) methyl-2H-1,4-benzodiazepin-2-one;

1-benzyl-7-chloro-1,3-dihydro-3(S)-(3'-indolyl) methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

7-chloro-1,3-dihydro-3(R)-(3'-indolyl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-thione;

1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl) methyl-2H-1,4-benzodiazepin-2-[N'-(3-thienoyl)] hydrazide;

1,3-dihydro-1-ethyl-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one;

1-cyclopropylmethyl-1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl) methyl-1-pentyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl) methyl-1-(3-methylbutyl)-2H-1,4-benzodiazepine-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-1-(2,2,2-trifluoroethyl)-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-1-(2-dimethylaminoethyl)-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-1-(ethoxycarbonylmethyl)-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one;

1-carboxymethyl-1,3-dihydro-5-(2-fluorophenyl)-3(R)-3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3(R)-[3'-(1'-p-chlorobenzyloylindolyl)methyl]-1-methyl-2H-1,4-benzodiazepin-2-one;

7-chloro-1,3-dihydro-3(R)-[3'(1'-benzylindolyl)methyl]-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-[1-hydroxy-1-(3'-indolyl)]methyl-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-1-methyl-5-phenyl-3-(RS)-(3-thienoyl)-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3-(RS)-[1-hydroxy-1-(3-thienyl)]methyl-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-[1-hydroxy-1-[3-(1-methylindolyl)]]-methyl-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one, two stereoisomers;

1,3-dihydro-3(RS)-(1-hydroxy-1-phenyl)methyl-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-[1-hydroxy-1-(2-thienyl)]methyl-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3-(RS)-hydroxy-1-methyl-5-phenyl-3-(3'-thienoyl)-2H-1,4-benzodiazepin-2-one;

1,5-dihydro-5-(RS)-hydroxy-1-methyl-5-phenyl-3-(3'-thienoyl)-2H-1,4-benzodiazepin-2-one;

7-chloro-1,3-dihydro-3(R)-[(2',3'-dihydro-2'-oxo-1'H-indol-3'-yl)methyl]-5-phenyl-2H-1,4-benzodiazepin-2-one;

7-chloro-1,3-dihydro-3(R)-[(3'-(2,4-dinitrophenyl)-imidazol-5'-yl)-methyl]-5-phenyl-2H-1,4-benzodiazepin-2-one;

7-chloro-1,3-dihydro-3(R)-(3'-imidazol-5'-yl)methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

3(RS)-[3'-(5'-Bromoindolyl)methyl]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one;

5-o-carboxyphenyl-1,3-dihydro-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-[3'-(5'-fluoroindolyl)methyl]-5-o-fluorophenyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-[3'-(6'-fluoroindolyl)methyl]-5-o-fluorophenyl-2H-1,4-benzodiazepin-2-one;

2-N-[2(RS),3-bis-(Bocamino)propanoyl]amino-2'-fluoro-benzophenone;

2-N-[2(RS),3-diphthalylaminopropanoyl]amino-2'-fluoro-benzophenone;

1,3-dihydro-5-(2'-fluorophenyl)-3(RS)-aminomethyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2'-fluorophenyl)-3(R)-(4-amino)butyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2'-fluorophenyl)-3(RS)-benzyloxy-carbonylaminomethyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2'-fluorophenyl)-3(RS)-(3-thiophene-carbonyl)aminomethyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2'-fluorophenyl)-3(RS)-(2-indole)-carbonylaminomethyl)-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2'-fluorophenyl)-3(RS)-(6'-chloro-pyrazinyl)aminomethyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2'-fluorophenyl)-3(RS)-aminomethyl-1-methyl-2H-1,4-benzodiazepin-2-one;

3(RS)-(2-indolecarbonylamino)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-3(RS)-[2-(3-indolyl)ethyl]amino-5-phenyl-2H-1,4-benzodiazepin-2-one;

3(RS)-[3-(3-indole)propionylamino]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one;

3(RS)-(3-indoleacetylamino)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one;

3(RS)-(Boc-L-tryptophanyl)amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one;

Z-1,3-dihydro-1-methyl-5-phenyl-3-(3-thienylmethylene)-2H-1,4-benzodiazepin-2-one;

E-1,3-dihydro-1-methyl-5-phenyl-3-(3-thienylmethylene)-2H-1,4-benzodiazepin-2-one;

3(RS)-(BOC-D-tryptophyl)amino-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one;

3(RS)-[4-(3-indole)butyrylamino]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-(benzyloxycarbonyl)aminomethyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepine;

1,3-dihydro-3(RS)-[3'-(thiophene)carbonyl]amino-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepine;

1,3-dihydro-3(RS)-(2-indolecarbonyl)aminomethyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepine;

1,3-dihydro-3(RS)-(2-L-hydroxy-2-phenylacetyl)amino-methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepine;

1-(2-cyanoethyl)-1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one;

1-(2-cyanoethyl)-1,3-dihydro-5-(2-fluorophenyl)-3(R)-[1'-(2-cyanoethyl)-3'-indolyl]-methyl-2H-1,4-benzodiazpin-2-one;

1-(2-carboxyethyl)-1,3-dihydro-5-(2-fluorophenyl)-3(R)-(3'-indolyl)methyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(R)-(3'-indolyl)methyl-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one-4-oxide;

1,3-dihydro-5-(2-fluorophenyl)-3-(RS)-(2-indolecarbonylamino)-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3(RS)-(2-indolecarbonylamino)-1-methyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-1-methyl-3(RS)-[2'-(1-methylindole)carbonylamino]-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-(4-nitrophenylcarbonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-(2-indolecarbonyloxy)-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3(RS)-(3-thiophene carbonylamino)-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-(3-indolecarbonylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-(4-thianaphtheneacetyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-(4-chlorophenylcarbonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-(4-methylphenylsulfonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1-carboxymethyl-1,3-dihydro-5-(2-fluorophenyl)-3(RS)-(2-indolecarbonylamino)-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-3(RS)-(5-fluoroindole-2-carbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-(3'-methylindenyl-2-carbonyl)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-(2-quinaldyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-(2-L-hydroxy-2-phenylacetyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-3(RS)-(5-chloroindole-2-carbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

(b.)

3(RS)-[N-(2-indolecarbonyl)-N-methylamino]-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-1-methyl-3(RS)-[2-(1-methylindole)carbonylamino]-5-phenyl-2H-1,4-benzodiazepin-2-one;

1-carboxymethyl-1,3-dihydro-3(RS)-(2-indolecarbonylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-3(RS)-(5-bromoindole-2-carbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

3(RS)-cinnamoylamino-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-(5-hydroxy-2-indolylcarbonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1-carboxamidomethyl-1,3-dihydro-3R-(3-indolylmethyl)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3-(RS)-(2-indolylmethylamino)-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-(phenylaminomethylcarbonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-3(RS)-(5-methoxyindole-2-carbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-3(RS)-(1-methylindole-2-carbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one;

1,3-dihydro-1-methyl-3(RS)-(4-chlorophenylcarbonyl)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-5-(2-fluorophenyl)-3(RS)-(2-benzofurancarbonylamino)-2H-1,4-benzodiazepin-2-one;

1-ethoxycarbonylmethyl-1,3-dihydro-3(RS)-(4-chlorophenylcarbonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1,3-dihydro-3(RS)-(4-chlorophenylcarbonyl)amino-5-phenyl-2H-1,4-benzodiazepine-2-one;

1,3-dihydro-1-methyl-3(RS)-(4-chlorophenyl-carbonyl)amino-5-phenyl-2H-1,4-benzodiazepin-2-one;

1-carboxymethyl-1,3-dihydro-3(RS)-(4-chlorophenyl-carbonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

3(RS)-(2(S)-tert-Butoxycarbonylamino-3-phenylpropanoylamino)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one;

3(RS)-(2(S)-tert-Butoxycarbonylamino-3-phenylpropanoylamino)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

3(R)- and 3(S)-(2(S)-Amino-3-phenylpropanoylamino)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

3(R)- and 3(S)-Amino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

3(R)- and 3(S)-Amino-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one;

3(S)-(-)-1,3-Dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

3(S)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(2-indole-carbonylamino)-1-methyl-2H-1,4-benzodiazepin-2-one;

3(R)-(-)-1,3-Dihydro-5-(2-fluorophenyl)-3-(2-indole-carbonylamino)-1-methyl-2H-1,4-benzodiazepin-2-one;

3(R)-(-)-1,3-Dihydro-3-(4-chlorobenzoylamino)-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one;

3(S)-(+)-1,3-Dihydro-3-(4-chlorobenzoylamino)-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one;

3(S)-(-)-1,3-Dihydro-3-(4-bromobenzoylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

3(R)-(+)-1,3-Dihydro-3-(4-bromobenzoylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

3(R)-(+)-1,3-Dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-3-(RS)-(2-indolinecarbonylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-(p-trifluoromethylbenzoylamino)-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-(p-methylbenzoylamino)-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-(p-methoxybenzoylamino)-2H-1,4-benzodiazepin-2-one;

3-(RS)-(o-Chlorobenzoylamino)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one;

3-(RS)-(o-Chlorobenzoylmethylamino-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

3-(RS)-(o-Chlorobenzoylamino)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

3-(RS)-(m-Chlorobenzoylamino)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one;

3-(RS)-(3,4-Dichlorobenzoylamino)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one;

3-(RS)-(p-Chlorobenzoylamino)1,3-dihydro-5-(2'-fluorophenyl)-1-methyl-4-oxo-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-Phenyl-3-(RS)-(4'-methylthiobenzoylamino)-2H-1,4-benzodiazepin-2-one;

1-3-Dihydro-3-(RS)-(4'-Fluorobenzoylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-Phenyl-3-(RS)-(4'-trifluoromethylbenzoylamino)-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-3-(RS)-(4'-tert-Butylbenzoylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one;

3-(RS)-(3,5-Dichlorobenzoylamino)1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one;

1-3-Dihydro-3-(RS)-(p-Hydroxybenzoylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one;

3-(RS)-(4'-Cyanobenzoylamino)1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one;

3(S)-(-)-3-(2-Chlorobenzoylamino)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

3(R)-(+)-3-(2-Chlorobenzoylamino)-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-3(RS)-(p-dimethylaminobenzoylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-3(RS)-(3,4-dimethoxybenzoylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

3(S)-(+)-3-(3-Bromobenzoylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-phenyl-3(RS)-(3-trifluoromethylthio-benzoylamino)-2H-1,4-benzodiazepin-2-one;

3(S)-(+)-3-(4-Bromobenzoylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one;

3(S)-(+)-3-(4-t-Butylbenzoylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-(2-fluorophenyl)-3(RS)-(pyrrole-2-carbonylamino)-2H-1,4-benzodiazepin-2-one;

3(S)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(4-iodo-benzoylamino)-1-methyl-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-3(RS)-(2-naphthoylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one;

3(S)-(-)-3-(2-Bromobenzoylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one;

3(S)-(+)-3-(4-Cyanobenzoylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-phenyl-3(RS)-(4-n-propylbenzoylamino)-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-phenyl-3(RS)-(4-phenylbenzoylamino)-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-3(RS)-(4-n-pentylbenzoylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-3(RS)-(1-naphthoylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one;

3(S)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(3-iodobenzoylamino)-1-methyl-2H-1,4-benzodiazepin-2-one;

3(R)-(-)-1,3-Dihydro-5-(2-fluorophenyl)-3-(3-iodobenzoylamino)-1-methyl-2H-1,4-benzodiazepin-2-one;

3(R)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(2-iodobenzoylamino)-1-methyl-2H-1,4-benzodiazepin-2-one;

3(S)-(-)-1,3-Dihydro-5-(2-fluorophenyl)-3-(2-iodobenzoylamino)-1-methyl-2H-1,4-benzodiazepin-2-one;

3(R)-(+)-3-(2-Bromobenzoylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one;

3(R)-(+)-3-(2-Chlorobenzoylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-(2-fluorophenyl)-3(RS)-phenylcarbonylamino-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-(2-fluorophenyl)-3(RS)-(2-chlorophenyl)-carbonylamino-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-(2-fluorophenyl)-3(RS)-benzyloxycarbonylamino-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-benzyloxycarbonylamino-2H-1,4-benzodiazepin-2-thione;

1-(4-Chlorophenyl)carbonyl-1,3-dihydro-5-(2-fluorophenyl)-3(RS)-(4-chlorophenyl)carbonylamino-2H-1,4-benzodiazepin-2-one;

1-(4-Chlorophenyl)carbonyl-1,3-dihydro-5-(2-fluorophenyl)-3(RS)-(4-chlorophenyl)carbonyloxy-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-(2-fluorophenyl)-3(RS)-(4-chlorophenyl)-oxy-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-(4-chlorophenyl)carbonylamino-2H-1,4-benzodiazepin-2-thione;

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-(2-indole) carbonylamino-2H-1,4-benzodiazepin-2-thione;
1,3-Dihydro-3(RS)-(4-chlorophenyl)aminocarbonylamino-2H-1,4-benzodiazepin-2-one;

6. A compound according to claim 1 which is 1-carboxymethyl-1,3-dihydro-3(RS)-(2-indolecarbonylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one.

7. A compound according to claim 1 which is (S)-(-)-1,3-dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.

8. A compound according to claim 1 which is (S)-(+)-1,3-dihydro-5-(2-fluorophenyl)-3-(2-indolecarbonylamino)-1-methyl-2H-1,4-benzodiazepin-2-one.

9. A compound according to claim 1 which is (S)-(+)-1,3-dihydro-3-(4-chlorobenzoylamino)-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one.

10. A compound according to claim 1 which is (S)-(-)-1,3-dihydro-3-(4-bromobenzoylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;
3(RS)-(2-indolecarbonylamino)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one;
1,3-Dihydro-3(RS)-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;
1,3-dihydro-1-methyl-3(RS)-[2-(1-methylindole)

carbonylamino]-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-1-methyl-3(RS)-(4-chlorophenylcarbonyl)-amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-(2-fluorophenyl)-3(RS)-(2-indolecarbonylamino)-1-methyl-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-(2-fluorophenyl)-1-methyl-3(RS)-[2'-(1-methylindole)carbonylamino]-2H-1,4-benzodiazepin-2-one;

3(R)-(-)-1,3-Dihydro-3-(4-chlorobenzoylamino)-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one;

3(S)-(+)-1,3-Dihydro-3-(4-chlorobenzoylamino)-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one;

3(R)-(+)-1,3-Dihydro-3-(4-bromobenzoylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

3(R)-(+)-1,3-Dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-(2-indolecarbonylamino)-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-3-(RS)-(2-indolecarbonyloxy)-5-phenyl-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-3-(RS)-(4-chlorophenylcarbonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1-Carboxymethyl-1,3-dihydro-5-(2-fluorophenyl)-3(RS)-(2-indolecarbonylamino)-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-3-(RS)-(5-fluoroindole-2-carbonylamino)-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

3-(RS)-Cinnamoylamino-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-(2-benzofurancarbonylamino)-2H-1,4-benzodiazepin-2-one;

1,3-Dihydro-1-methyl-3-(RS)-(4-chlorophenylcarbonyl)-amino-5-phenyl-2H-1,4-benzodiazepin-2-one;
1-Carboxymethyl-1,3-dihydro-3-(RS)-(4-chlorophenylcarbonyl)amino-5-(2-fluorophenyl)-2H-1,4-benzodiazepin-2-one;
1,3-Dihydro-5-(2-fluorophenyl)-3-(RS)-(p-trifluoromethylbenzoylamino)-2H-1,4-benzodiazepin-2-one;
3(S)-(+)-3-(3-Bromobenzoylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one;
3(S)-(+)-3-(4-Bromobenzoylamino)-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one;
3(S)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(4-iodobenzoylamino)-1-methyl-2H-1,4-benzodiazepin-2-one;
1,3-Dihydro-3(RS)-(2-naphthoylamino)-5-phenyl-2H-1,4-benzodiazepin-2-one;
3(S)-(+)-1,3-Dihydro-5-(2-fluorophenyl)-3-(3-iodobenzoylamino)-1-methyl-2H-1,4-benzodiazepin-2-one; or
3(R)-(-)-1,3-Dihydro-5-(2-fluorophenyl)-3-(3-iodobenzoylamino)-1-methyl-2H-1,4-benzodiazepin-2-one;
3(R)-(-)-1,3-Dihydro-5-(2-fluorophenyl)-3-(2-indolecarbonylamino)-1-methyl-2H-1,4-benzodiazepin-2-one.

11. A pharmaceutical composition useful for treating gastrointestinal disorders, central nervous system disorders, or regulating appetite in mammals, characterized in that it contains as pharmaceutically active ingredient at least one compound of formula I, according to claim 1, or a pharmaceutically acceptable salt or pharmaceutically acceptable quaternary ammonium salt of the compounds of formula I.

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12. A pharmaceutical composition according to claim 11 characterized in that it contains as active ingredient a compound of formula I wherein:

R^1 is H, loweralkyl, or $-(CH_2)_mCOOR^6$;

R^2 is substituted or unsubstituted phenyl (wherein the substituents may be 1 or 2 of halo, loweralkyl, loweralkoxy, carboxyl, carboxyloweralkyl, nitro, $-CF_3$, or hydroxy), or $-(CH_2)_mCOOR^6$;

R^3 is $-(CH_2)_nR^7$, $-(CH_2)_nCHR^7$ (OH),

$-(CH_2)_nCR^7$ (O), $-(CH_2)_nNH(CH_2)_qR^7$,

$-(CH_2)_nNHCHCOOR^6$ (R^7, $(CH_2)_q$), $-(CH_2)_nNHC(CH_2)_qR^7$ (O),

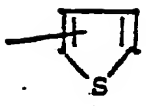
$-NH(CH_2)_{2-3}NHR^7$, $-(CH_2)_nNHCCHCH_2R^7$ (O, $NHCOOR^{14}$),

$-NH(CH_2)_{2-3}NHCOR^7$, or $-(CH_2)_nNHCNH(CH_2)_nR^7$ (O);

R^4 and R^5 are independently H or loweralkyl;

R^6 is H or loweralkyl;

R^7 is α- or β-naphthyl,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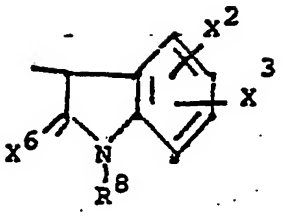
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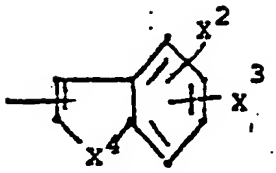
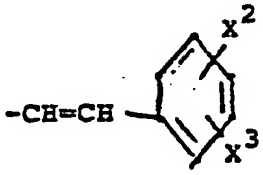
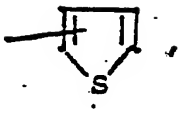

,

substituted or unsubstituted phenyl wherein the substituents may be 1 to 2 of halo, $-NO_2$, -OH, $-NR^4R^5$, loweralkyl, loweralkoxy, CF_3, lower alkylthio, CN, C≡CH, SCF_3, $O\overset{O}{\overset{\|}{C}}CH_3$, $OCHF_2$, or SPh,


, or

R^8 is H, loweralkyl, or $-COCHNHCOOR^{11}$;
CH_2R^{12}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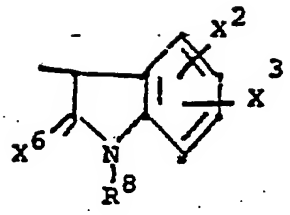
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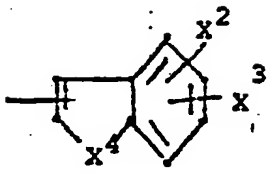
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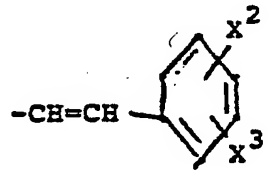
substituted or unsubstituted phenyl wherein the substituents may be 1 to 2 of halo, $-NO_2$, -OH, $-NR^4R^5$, loweralkyl, loweralkoxy, CF_3,

lower alkylthio, CN, C≡CH, SCF_3, $O\overset{O}{\overset{\|}{C}}CH_3$, $OCHF_2$, or SPh,


, or

R^8 is H, loweralkyl, or $-COCHNHCOOR^{11}$;
CH_2R^{12}

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R^9 and R^{10} are independently H, -OH, or $-CH_3$;
R^{11} and R^{12} are independently loweralkyl;
R^{13} is H, O, loweralkyl, or acyl;
R^{14} is loweralkyl;
R^{15} is H or loweralkyl;
m is 1-4;
n is 0-4;
p is 0 when its adjacent --- is unsaturated and 1 when its adjacent --- is saturated, except that when R^{13} is O, p=1 and --- is unsaturated;
q is 0-4;
r is 1 or 2;
X^1 is H, $-NO_2$, CF_3, CN, OH, loweralkyl, halo, loweralkylthio, loweralkoxy, $-(CH_2)_nCOOR^6$, or $-NR^4R^5$;
X^2 and X^3 are independently H, -OH, $-NO_2$ halo, loweralkylthio, loweralkyl, or loweralkoxy;
X^4 is S, O, or NR^8;
X^6 is O or HH;
X^7 is O;
--- is a saturated or unsaturated bond

or a pharmaceutically acceptable salt or pharmaceutically acceptable quaternary ammonium salt of said compounds of formula I.

13. Pharmaceutical composition according to one of the claims 10 - 12 characterized in that it contains as active ingredient a compound according to one of the claims 3 - 10.

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14. A pharmaceutical composition according to one of the claims 11 - 13, characterized in that it contains as further component a pharmaceutically acceptable carrier.

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